Department of Radiology and Biomedical Imaging
University of California, San Francisco School of Medicine
presents

8th International Breast Density and Cancer Risk Assessment Workshop (Non-CME)

June 7-9, 2017
Hotel Kabuki
San Francisco, California

Course Directors
Karla Kerlikowske, MD
John Shepherd, PhD
University of California, San Francisco

UCSF University of California, San Francisco School of Medicine

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Department of Health Sciences Research, Mayo Clinic, Rochester, MN

Isabel dos Santos Silva MD MSc PhD
Professor of Epidemiology, University of London, London, UK.

Overview:
A high amount of dense breast tissue has been shown to be one of the strongest risk factors for breast cancer, although the specific reason(s) for this is not known. Recent legislation in several states, including California, requires reporting of breast density to women with dense breasts undergoing mammography. Ideally, prior to enacting legislation, there would be guidelines on how best to measure breast density, what risk model to use that includes breast density to report breast cancer risk, as well as a standardized form to communicate this information. Research is ongoing to understand how different technologies that measure breast density relate to both breast cancer detection and breast cancer risk.

The 2017 Conference will feature three days of presentations consisting of approximately 16 internationally-recognized invited speakers, and 10 oral presentations from submitted abstracts. In addition, there will be a poster session on Thursday and Friday to highlight research from attendees.

Objectives:
The participants will leave the workshop having gained tangible understanding and insights to the clinical applications and research topics in breast density. Specifically, the participants will have a complete overview of the current trends, capabilities, and limitations of risk factors from mammographic imaging. Second, the participants will have a key understanding of how or if these imaging risk factors are independent from other clinical and genetic risk factors. Third, the participant will know the key needs and research breakthroughs needed to best identify women at high risk of breast cancer.

Acknowledgement of Commercial Support

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General Information

Evaluation / Certificate of Attendance
After the meeting, you will receive an email from Qualtrics@ucsf.edu to complete your online Evaluation / Certificate of Attendance. Please make sure that you add this email to your safe senders list or you may not receive the email notifications and certificate. The Qualtrics system will send you reminders to complete your Evaluation / Certificate of Attendance until it is completed.

Upon completion, your certificate of attendance will be automatically generated to print and/or email yourself a copy. For smartphone users, you may want to take a photo of your certificate as some settings prevent you from emailing the certificate.

The link will be available for 30 days after the last day of the course. However, after that date the link will expire and you will no longer be able to claim your credits online. You must then contact the Office of CME at registration@ocme.ucsf.edu to receive your certificate and a $15 administrative fee may be applied.

Speaker Survey
On the first morning of the conference you will receive a link for the speaker survey. Please be sure to complete your speaker evaluation online at the conclusion of the course as we appreciate your feedback and use it to plan future courses.

Security
We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during lunch or breaks or overnight.

Exhibits
Industry exhibits will be available outside the ballroom in the Spring Room during breakfasts and breaks, and lunches.

Poster Sessions
The Poster Sessions will take place in the Sakura Ballroom on the lobby level of the hotel. Session 1 will be held on Thursday, and Session 2 will be held on Friday.

Final Presentations
A link to PDF versions of the final presentations will be sent via e-mail approximately 3 – 4 weeks post course. Only presentations that have been authorized for inclusion by the presenter will be included

HOTEL KABUKI

SAN FRANCISCO

Welcome to Hotel Kabuki. For your convenience, we have compiled a list of our favorite nearby food and drink recommendations. Please contact one of our Hosts for additional information.

Japan Center Restaurants

- **Benihana** (Japanese)$$: Japan Center Mall- Kintetsu Building 415-563-4844 (*½ block*)
- **Isobune Sushi** (Japanese)$$: Japan Center Mall- Nihomachi Building 415-563-1030 (*½ block)*
- **Mifune Don** (Japanese)$: Japan Center Mall- Miyako Building) 415-346-1993 (*½ block)*
- **Sapporo-ya** (Japanese)$$: Japan Center Mall-Kinokuniya Building 415-563-7400 (*1 block)*

Fillmore Street Restaurants

(two blocks west on Post Street, then left or right on Fillmore)

- **Dosa** (Southern Indian)$$: 1700 Fillmore Street at Post, 415-441-3672 (*2 blocks)*
- **Out the Door** (Vietnamese)$$: 2232 Bush Street at Fillmore, 415-923-9575 (*5 blocks)*
- **Florio** (French-Italian brasserie)$$: 1915 Fillmore Street between Bush and Pine, 415-775-4300 (*5 blocks)*
- **Roam Artisan Burgers** (American)$: 1923 Fillmore Street between Bush and Pine, 415-800-7801 (*5 blocks)*
- **Woodhouse Fish Co.** (American Seafood)$$: 1914 Fillmore Street between Bush and Pine, 415-437-2722 (*5 blocks)*
- **SPQR** (American/Italian)$$$: 1911 Fillmore Street between Bush and Pine, 415-771-7779 (*5 blocks)*
- **The Grove** (American Café)$$: 2016 Fillmore Street between Pine and California, 415-474-1419 (*6 blocks)*
- **Pizzeria Delfina** (Neapolitan Pizzeria)$$: 2406 California Street at Fillmore, 415-440-1189 (*7 blocks)*
- **1300 on Fillmore** (Refined Soul Food and Cocktails) $$$: 1300 Fillmore St, 415-771-7100 *(5 blocks)*
- **State Bird Provisions (**Award-winning, American small plates) $$$: 1529 Fillmore St at Geary, 415-795-1272 *(4 blocks)*

Cocktails

- **Benihana** (Japanese)$$: Japan Center Mall- Kintetsu Building 415-563-4844 (*½ block*)
- **1300 on Fillmore** (Refined Soul Food and Cocktails) $$$: 1300 Fillmore St, 415-771-7100 *(5 blocks)*
- **The Social Study** (Wine and Craft Beer) $: 1795 Geary Blvd, 415-292-7417 *(4 blocks)*
- **Harry's Bar** (After-work pub grub and game-watching) $$: 2020 Fillmore St, 415-921-1000 *(6 blocks)*
- **Palmer's Tavern** (Classic Cocktails and American fare) $$: 2298 Fillmore St, (415) 732-7777 (*8 blocks)*

Additionally, delivery services are available including **Eat24** (eat24hours.com) and **GrubHub** (grubhub.com). To ensure our guests' security we ask that food-delivery services check-in with the Front Desk upon arrival.

Wednesday, June 7, 2017

8:00 am	*Registration and Continental Breakfast*	
Clinical Aspects of Breast Density, Part I		Moderator: John Shepherd
9:00	**Introduction and Overview**	John Shepherd
9:15	**Breast Density in the Tomosynthesis World**	Sophia Zackrisson
10:00	**Diagnostic Performance of Tomosynthesis and Breast Ultrasonography in Women with Dense Breasts: A Prospective Comparison Study**	Jung Min Chang
10:45	*Coffee Break*	
11:15	**The Role of MRI in Screening for Breast Cancer in Dense Breasts: The DENSE Trial**	Carla van Gils
12:00 pm	*Lunch*	
Clinical Aspects of Breast Density, Part II		Moderator: Jennifer Harvey
1:00	**Abbreviated MRI and the Dense Breast**	Christopher Comstock
1:45	**Managing Women with Dense Breast in Europe, Asia- Austrian Radiologists presents their US/Mammo**	Thomas Helbich
2:30	*Coffee Break*	
3:00	**Communicating Risk and Density to Women**	Carmen Radecki Breitkopf
4:00	**Panel Discussion and Questions**	
4:15	**Adjourn**	
4:15-6:15	***Networking Reception***	

Thursday, June 8, 2017

8:00 am	*Registration and Continental Breakfast*	
Breast Density Workshop, Part I		Moderator: Isabel Dos Santos
9:00	**Overview**	
9:15	**The Measurement Challenge**	Jennifer Stone
9:55	**Abstract Proffered Talk 1:** A Comparison of Volpara Mammographic Breast Density with UST Sound Speed Measurements	Mark Sak
10:15	**Abstract Proffered Talk 2:** Association of Breast Figroglandular Volume Spatial Distributions with Breast Cancer Risk Factors	Serghei Malkov
10:35	*Coffee Break*	
11:05	**Masking and Breast Density – Summary of Masking Efforts**	Nico Karssemeijer
11:45	**Volumetric and BI-RADS Density Measures and Interval Cancers**	Karla Kerlikowske
12:25	*Lunch*	
1:25	**Poster Session- Odd Numbers**	
Breast Density Workshop, Part II		Moderator: Nico Karssemeijer
2:10	**Quantitative Imaging Phenotyping of Breast Cancer Risk**	Aimilia Gastounioti
3:10	**Abstract Proffered Talk 3:** An Open Labelled Evaluation of Subcutaneous Combined Testosterone / Anastrozole Implants in Pre-Menopausal Women with High Volumetric Mammographic Breast Density (HMBD)	Stephen Birrell
3:40	Coffee Break	
4:20	**Microcalcifications, Masses, Density, BMI, HRT, and Family History of Breast Cancer Used to Create a 2-Year Risk Model for Use in**	Mikael Eriksson

	Individualized Screening	
4:40	**Abstract Proffered Talk 4:** Rapid Reductions in Breast Density Following Tamoxifen Therapy as Evaluated by Whole Breast Ultrasound Tomography	Gretchen Gierach
5:00	**Abstract Proffered Talk 5:** Mandatory Breast Density Reporting in Massachusetts: Patient Understanding and Effects on Screening Intentions	Erica Warner
5:15	**Panel Discussion and Questions**	
	Adjourn	

Friday, June 9, 2017

8:00 am	*Continental Breakfast*	
Breast Cancer Risk Assessment - Putting it all together, Part I		Moderator: Karla Kerlikowske
9:00	**Overview**	
9:15	**Involution and Breast Density**	Mark Sherman
9:55	**Abstract Proffered Talk 6:** Using Convolutional Neural Networks to Delineate Pathological Correlates of Mammographic Breast Density from Diagnostic Image-Guided Breast Biopsies	Maeve Mullooly
10:15	**Abstract Proffered Talk 7:** Large Breast Cancers in Women Attending Regular Screening: Risk Factors and Implications for Prognosis	Fredrik Strand
10:35	*Coffee Break*	
11:05	**Micro-Structure and Micro-Mechanics of Breast Density**	Michael Sherratt
11:45	**iCARE Breast Cancer Risk Model Development and Validation**	Montse Garcia-Closas
12:25 pm	**Lunch**	
1:25	**Poster Session - Even Numbers**	
Breast Cancer Risk Assessment - Putting it all together, Part II		Moderator:
2:25	**Using a Polygenic Risk Score and Breast Density to Predict Interval Cancers**	Yiwey Shieh
3:05	**Abstract Proffered Talk 8:** Genome-Wide Association Study Identifies Novel Loci for Mammographic Breast Density	Weiva Sieh
3:25	*Coffee Break*	
3:55	**Integrating Breast Density and SNP Scores in to the Tyrer-Cuzick Model**	Jack Cuzick
4:35	**Abstract Proffered Talk 9:** Evaluation of the Tyrer-Cuzick Breast Cancer Risk Model with BIRADS Density in a Screening Cohort from Washington State	Adam Brentnall
4:55	**Abstract Proffered Talk 10:** Population-Based Assessment of the Effect of MRI Background Parenchymal Enhancement on Future Primary Breast Cancer Risk	Vignesh Arasu
5:15	**Panel Discussion and Questions**	
5:30pm	*Adjourn*	

8th International Breast Density and Cancer Risk Assessment Workshop Course Roster		
Abdolell	Mohamed	Halifax, NS, Canada
Acerbi	Irene	San Francisco, CA
Arasu	Vignesh	San Francisco, CA
Astley	Susan	Manchester, United Kingdom
Atakpa	Emma	London, United Kingdom
Bakker	Marije F	Utrecht, Netherlands
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Brentnall	Adam	London, United Kingdom
Byrne	Celia	Bethesda, MD
Chang	Jun Min	Seoul, South Korea
Clarke	Christina	Menlo Park, CA
Comstock	Christopher E.	New York, NY
Conant	Emily	Philadelphia, PA
Cummings	Steven R.	San Francisco, CA
Cuzick	Jack	London, United Kingdom
De Lange	Stéphanie	Utrecht, Netherlands
Dos Santos Silva	Isabel	London, United Kingdom
Engmann	Natalie	San Francisco, CA
Eriksson	Mikeal	Taby, Sweden
Garcia-Cloes	Montse	Rockville, MD
Gascard	Philippe Daniel	San Francisco, CA
Gastounioti	Aimilia	Philadelphia PA
Ghosh	Karthik	Rochester, MN
Gierach	Gretchen	Bethesda, MD
Graff	Rebecca	San Francisco, CA
Habel	Laurel	Oakland, CA
Hada	Manila	Gaithersburg, MD
Harris	Holly	Seattle, WA
Harvey	Jennifer A.	Charlottesville, VA
Helbich	Thomas	Vienna, Austria
Hopper	John L	Carlton, VIC, Australia
Hruska	Carrie B	Mantorville, MN
Ikeda	Debra M.	Stanford, CA
Karssemijer	Nico	Nijmegen, Netherlands
Keller	Brad M	Newark, DE
Kerlikowske	Karla	San Francisco, CA
Kontos	Despina	Havertown, PA

Lee	Eunjung	Los Angeles, CA
Lee	Jiyon	Scarsdale, NY
Lee	Karen Ann	New York, NY
Ling	Jennie	San Francisco, CA
Lipson	Jafi	Palo Alto, CA
Malkov	Serghei	San Francisco, CA
Miglioretti	Diana	Davis, CA
Morris	Elizabeth A.	New York, NY
Mullooly	Maeve	Bethesda, MD
Northey	Jason	San Francisco, CA
Oh	Hannah	New Brunswick, NJ
Ohikere	Kabiru Ozovehe	San Leandro, CA
Owens	Jessica	Menlo Park, CA
Pereira	Ana	Santiago, Chile
Puvanesarajah	Samantha	Chapel Hill, NC
Radecki-Breitkopf	Carmen	Rochester, MN
Reitherman	Richard	Newport Beach, CA
Rice	Megan	Boston, MA
Sak	Mark	Novi, MI
Sechopoulos	Ioannis	Arnhem, Netherlands
Shepherd	John	San Francisco, CA 94118
Sherman	Mark	Rochester, MN
Sherratt	Michael	Manchester, United Kingdom
Shieh	Yiwey	San Francisco, CA
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Strand	Fredrik	Stockholm, Sweden
Talbot	Pam	Halifax, NS, Canada
Tamimi	Rulla	Boston, MA
Tehranifar	Parisa	New York, NY
Terry	Mary Beth	New York, NY
Toriola	Adetunji T.	St. Louis, MO
van Gils	Carla	Utrecht, The Netherlands
Van 'T Veer	Laura	San Francisco, CA
Wang	Chao	London, United Kingdom
Warner	Erica T.	Boston, MA
Wu	Anna H	Los Angeles, CA
Zackrisson	Sophia	Malmö, Sweden

Clinical Aspects of Breast Density

June 7, 2017

Sophia Zackrisson

Breast Density in the Tomosynthesis World

It is well known that digital mammography (DM) has limitations in detecting breast cancers, especially in women with dense breasts. Studies show that up to 30% of the cancers in screening may not be detectable with DM, mainly due to the overlapping tissue effect, i.e. dense breast tissue or the so-called anatomical noise obscuring the tumor on the 2-dimensional images. Digital breast tomosyntesis (DBT) is an emerging pseudo 3D technique in breast imaging based on the acquisition of low-dose projections over a limited arc, reconstructed into a volume of generally up to 50 images of the breast. This reduces the overlapping tissue effect and hence tumors may be more easily detected with DBT. Data from several large European prospective population-based screening trials is now available and show that the use of DBT alone or in combination with two-view DM or synthetic DM substantially improved cancer detection compared to two-view DM screening. In other settings, mainly in the US, retrospective studies with the combination of DBT and DM has been conducted with large reductions in recall rates as the main effect. The majority of the trials and studies report increased breast cancer detection across all breast density categories, although with the highest incremental breast cancer detection in the range of 1.4-5.0/1000 screens in women with dense breasts. In this presentation, the use of DBT in screening will be presented and discussed in terms of screening performance measures and breast density and what needs to be further investigated before DBT can fully implemented in routine screening.

Title of Abstract:

Diagnostic performance of tomosynthesis and breast ultrasonography in women with dense breasts: a prospective comparison study

Presenting Authors Full Name: Jung Min Chang

Institution: Seoul National University hospital

Additional Author's Names as to be Published:
Won Hwa Kim, Joongyub Lee, Woo Kyung Moon

Purpose:
Tomosynthesis or ultrasound may overcome the limitation of mammography for breast cancer diagnosis in women with dense breasts. We evaluated the diagnostic performance of tomosynthesis compared with whole breast ultrasound as an adjunct to digital mammography.

Method:
From June 2013 to June 2014, we conducted a prospective study of 778 women with dense breasts at a single tertiary institution to test our hypothesis that tomosynthesis is non-inferior to ultrasound as an adjunct to mammography. All women underwent digital mammography with tomosynthesis and ultrasound examinations for screening and diagnostic purposes. Two independent readings for tomosynthesis and ultrasound were performed by 12 radiologists. The primary end point was overall diagnostic accuracy, as assessed by area under receiver operating characteristic curve (AUC) with a non-inferiority margin of 0·1. Secondary end points included sensitivity, specificity, and predictive values. This study was registered, ClinicalTrials.gov No. NCT01910103.

Results:
Among the participants, 140 were diagnosed with cancer (mean size, 1·6 cm; 115 invasive and 25 in situ cancers). Based on the AUC, the non-inferiority of tomosynthesis to ultrasound was established in the overall group (0·933 vs. 0·964; difference, -0·031; 95% confidence interval [CI], -0·055 to -0·006), heterogeneously dense subgroup (0·949 vs. 0·969; difference, -0·020; 95% CI, -0·042 to 0·002), and asymptomatic subgroup (0·912 vs. 0·934; difference, -0·022; 95% CI, -0·075 to 0·030). However, this was not established in the extremely dense breast subgroup (0·843 vs. 0·931; difference, -0·089; 95% CI, -0·192 to 0·013). The sensitivity was lower for tomosynthesis than for ultrasound (91·4% vs. 96·4%, p=·039). However, the specificity (84·2% vs. 71·1%, p<·0001) and

positive predictive value (58·7% vs. 45·0%, p<·0001) was higher for tomosynthesis than for ultrasound.

Conclusion:
Tomosynthesis was non-inferior to ultrasound as an adjunct to mammography for diagnosing breast cancer. However, higher cancer detection rate was noted for US especially in extremely dense breasts.

Title of Abstract: The role of MRI in Screening for Breast Cancer in Dense Breasts: the DENSE trial

Presenting Authors Full Name: Carla H. van Gils, PhD

Institution: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

MRI is the most sensitive breast cancer imaging technique currently available and recommended for screening women with high breast cancer risk. Women with dense breasts have a moderately increased breast cancer risk. In addition, their dense tissue limits the detection of a tumor with mammography and therefore additional screening with MRI could provide a solution for these women as well. However, MRI is not included in screening recommendations for women with dense breasts. The effects of MRI, and also those of other supplemental imaging methods, on breast cancer outcomes remain as yet unclear due to a lack of comparative studies with interval breast cancer rates, stage at diagnosis or breast cancer mortality as the outcome.

In this presentation I will outline the present evidence for MRI screening in women with dense breasts, and indicate which type of evidence is still needed to proof its additional value.

DENSE, a large randomized controlled trial, that we are currently conducting, has been designed to deliver this proof. It investigates the value of additional MRI compared to usual screening practice, in women with extremely dense breasts and a negative digital mammography. Women are included solely on the basis of their breast density. A fully automatic and validated method is used to estimate mammographic density. The primary outcome is a difference in interval cancer rates between the two arms, the best proxy for a difference in breast cancer mortality. These results will become available in 2018.

I will present our experiences in setting up the trial and explain why evidence from randomized trials and interval cancers is essential to answer the question. I will show the progress of the trial and give a description of the participants and their risk profiles. I will show results on the willingness of women to participate in such trial and adhere to it in subsequent screenings, and also on how they experience the risk-based supplemental screening.

Abbreviated MRI and the Dense Breast

Christopher Comstock

NOTES

Managing Women with Dense Breast in Europe, Asia- Austrian Radiologists present their US/Mammo screening program

T. Helbich, MD; Department of Biomedical Imaging & Image guided Therapy, Medical University of Vienna

The sensitivity and specificity of mammography are limited in highly fibroglandular /dense breasts. Digital mammography provides increased sensitivity in young women and those with moderately dense breasts, and digital three-dimensional mammography (Tomosynthesis) promises further improvement. For women with the densest breasts, however, radiography is unlikely to be the optimum solution. MRI, although not affected by breast density, is expensive and access is often limited. Ultrasonography is attractive for breast cancer screening because, likewise, it is not impaired by breast density, and it avoids the use of ionizing radiation and the need for breast compression. Nevertheless, enthusiasm for the use of ultrasonography has been limited because its specificity has been much lower than that of mammography, but technical developments have given rise to sharper, more informative images. These improvements foster the use of ultrasound particular in those women with higher breast density. Different trials have been preformed and promising results have been reported.

This talk will focus on benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. Will present the first results of Asian trials and will introduce the breast screening program of Austria which includes the use of mammography and ultrasound.

Title of Abstract: Communicating Risk and Density to Women

Presenting Authors Full Name: Carmen Radecki Breitkopf, PhD

Institution: Mayo Clinic

Additional Author's Names as to be Published:

Purpose: Breast cancer is the most common cancer among Latinas and the leading cause of cancer mortality in that population, accounting for 16% of all cancer deaths. Efforts to inform Latinas about screening options to improve early detection of breast cancer and educate women who are at higher risk are important and remain understudied, particularly among less acculturated Latinas. As more is known about the association between breast cancer risk and mammographic breast density, and in response to lobbying by patient advocates, an increasing number of US states have adopted legislation that mandates written notification of breast density along with screening mammography results. Examination of dense breast notification letters has shown variability in content, understandability, and readability across the 23 states with notification laws such that the particular information that a woman receives is dependent upon the state in which she lives.

The language that is used to communicate breast density information has been dictated by policy and legal experts and is not informed by evidence from behavioral and communication science. Evidence suggests that particular communication styles and visual displays for communicating risk information can enhance patient understanding. However, ethnic minorities are often not included in sufficient numbers to contribute to the body of evidence on which the recommendations surrounding cancer risk communication are based. Culturally consistent, plain-language communication is essential, particularly among Latinas with limited English proficiency. Additionally, there is greater benefit from multi-faceted interventions for patients with lower health literacy that involve multiple modalities through which health information is presented and received.

The overall purpose of this study is to evaluate whether educational enhancement of breast density notification is beneficial in populations known to be vulnerable to health disparities such as racial/ethnic minorities and those with lower health literacy, limited English proficiency, and socioeconomic disadvantage. Specifically, this study will assess important psychological and behavioral outcomes of emerging state mandates that women undergoing screening mammography be informed of their breast density and its impact on breast cancer risk.

Method: This study is an ongoing, prospective, 3-arm randomized trial comparing behavioral and psychological outcomes among Latinas who receive notification per current clinical practice (usual care) relative to two educationally-enhanced approaches that are theory informed, culturally consistent, and novel in this setting. A total of 2,000 women (primarily Latinas) who present for screening mammography in a partnering

federally qualified health center (FQHC) in Arizona will be randomized to one of three different approaches to breast density notification (study groups) that vary on the communication style and the presentation of risk information: mailed notification (usual care) *vs.* mailed notification plus written breast density educational materials (enhanced) *vs.* mailed notification, written breast density educational materials, plus verbal explanation and education by a lay health educator/*promotora* (interpersonal).

Critical to testing our intervention is the ability to measure potential mechanisms through which written or verbal information influences motivation and behavior related to breast cancer screening, as well as potential moderating factors such as depression and breast cancer worry that, among Latinas, are linked to diagnostic delays in the context of mammography. Thus, our study includes a comprehensive set of longitudinal outcome measures including patient-reported outcomes (anxiety, depression, knowledge and understanding of breast density, perceived risk of breast cancer, breast cancer worry, self-efficacy) and behavioral outcomes (continued adherence to mammography screening, discussion of breast density with a health care provider, uptake of supplemental screening). Qualitative inquiry related to process and outcomes of the *promotora* intervention and cost analysis related to its implementation will enhance our understanding of the intervention's delivery in practice and its transferability to other health care settings.

Results: This study is currently underway, thus trial results are unknown. During this presentation, study participant characteristics will be described and study measures (patient-reported, process, and outcome) and intervention materials will be shared. Perspectives of health care providers regarding density notification and its anticipated impact on clinical practice were captured qualitatively at this FQHC shortly after Arizona passed density legislation; these findings informed the design of the intervention for this clinical setting and will also be presented.

Conclusion: The effect of providing women with written notification about their breast density and its impact on breast cancer risk, absent other clinical or contextual information, may have unintended consequences, particularly among Latinas with lower health literacy and limited resources, including resources to pursue supplemental breast screening. Receiving breast density results in the context of an interpersonal conversation in which a lay educator delivers information dynamically, corrects misperceptions, provides personal and social motivation to act, and builds self-efficacy for behavioral performance is likely to be more effective than factual information delivered only in writing (enhanced study group), or notification-only (usual care group). Our results are intended to build the evidence base in the area of cancer risk communication and offer empirically-tested, generalizable educational strategies for delivering density information in limited-resource settings to vulnerable populations.

Breast Density Workshop

June 8, 2017

The Measurement Challenge

Presenting Author: Jennifer Stone, Centre for Genetic Origins of Health and Disease, Curtin University and the University of Western Australia

Author List: Daniela Bond-Smith[1], Cameron Wellard[2], Grant Lee[2], Ariane Chan[3], Jack Cuzick[4], Jennifer Harvey[5], Ralph Highnam[3], Meng-Kang Hsieh[6], Despina Kontos[6], Shivaani Mariapun[7], Kevin Nguyen[2], Carolyn Nickson[2], Kathy Repich[5], Daniel Schmidt[2], Soo-Hwang Teo[7], Giska Ursin[8], Chao Wang[4], Valerie McCormack[9], John Shepherd[10], Isabel dos Santos Silva[11], Mads Nielsen[12], John Hopper[2], Jennifer Stone[1]

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Purpose: There are multiple methods of measuring features from mammographic images that are potentially useful in a screening setting to predict breast cancer risk and tailor screening recommendations. However, it is unclear which measurement(s) provides the "best" predictor of this risk. The aim of The Measurement Challenge is to facilitate the measurement of mammographic density and other mammographic features from a large pooled breast cancer case-control set of full-field digital mammograms (FFDM) using as many methods as possible, for the purposes of the comparison of their **predictions of breast cancer risk**.

Method: Raw and processed FFDMs and corresponding core data from 1468 cases and 1747 controls were obtained from Australia (n=465 and 464, respectively), Malaysia (n=202 each), the United Kingdom (n=403 and 683, respectively) and the United States (n=398 each). Each case-control set was randomly split in half. The data and images from the first half were designed to be used as a "training set" to allow training (if desired) and included information regarding case-control status. The second half was designed to be the "test set" in which Challengers were blind to case-control status. Both sets of images were securely transferred to seven Challengers, of whom BIOMEDIQ, Cumulus, Libra, MMTEXT, and Volpara provided a total of 14 measurements (percent and absolute density as well as other scores) from the test set in time to be included in the current analysis. Logistic regression was used to estimate the association between the mammographic measures and breast cancer risk adjusted for all available covariates including age, BMI, ethnicity, site of mammography, image type (raw/processed) and manufacturer. The change in odds per adjusted standard deviation (OPERA) was estimated using age and BMI adjusted measures in the auxiliary regression. The receiver operating characteristic (ROC) curve was used to assess discrimination as well as area under the curve (AUC) statistics.

Results: To be presented at the meeting.

Conclusion: The Measurement Challenge is an ongoing collaboration and provides a unique annotated platform for timely and prompt assessment of new methods as they will become available in the future. Expansion of The Challenge to include larger data sets across different designs and technologies, and to consider other outcomes, could more rapidly advance the clinical implementation of densitometry to help lower the impact of breast cancer.

A Comparison of Volpara Mammographic Breast Density with UST Sound Speed Measurements

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Purpose:
Ultrasound tomography (UST) produces sound speed maps of breast tissue. Using these images, the volumetrically averaged sound speed can be used as a surrogate of breast density. Volpara produces automated measures of mammographic breast density. A direct comparison between the two measures has yet to be made.

Method:
A cohort of 183 women had received both a UST scan and a Volpara breast density reading of their mammogram. Volpara mammographic measures of percent density and dense volume were recorded from mammographic reports. The whole volume sound speed along with measures of dense volume and UST percent density (USTPD) were measured from the UST ray images using a semi-automated masking algorithm. Corresponding density measures were then compared using standard statistical techniques.

Results:
Spearman correlations between the UST and the Volpara density measures ranged from moderate to strong, rs = 0.787 for UST average sound speed vs Volpara PD, rs = 0.582 for USTPD vs Volpara PD and rs = 0.410 for UST vs Volpara dense volume. For some women, there was a significant time delay between the UST scan and the analyzed mammogram so the dataset was filtered such that the UST scan occurred within 100 days of the mammogram. For the 100 scans that fit this time constraint, the Spearman correlations increased, rs = 0.836 for UST average sound speed vs Volpara PD, rs = 0.608 for USTPD vs Volpara PD and rs = 0.415 for UST vs Volpara dense volume.

Conclusion:
This preliminary analysis shows that breast density measures made from UST sound speed images and made with Volpara correlate strongly. The relationships between Volpara and UST were stronger than previous results relating UST and mammographic measures made using Cumulus. Additional analysis is still needed to fully explore the relationship between the two breast density measures.

Association of Breast Figroglandular Volume Spatial Distributions with Breast Cancer Risk Factors

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Purpose:
The purpose of this study was to determine association of breast cancer risk and risk factor with spatial distribution of fibroglandular tissue volumes.

Method:
The film mammograms of 275 invasive and DCIS cancers and 825 controls matched by age, race/ethnicity and mammography system were used. We compared voxel-based morphometry among cases and controls and breast cancer risk factors including race/ethnicity, menopausal status, age at first birth, body-mass index (BMI), and prior history of biopsy among controls. We used the single x-ray absorptiometry method to obtain pixel-by-pixel values of volumetric breast densities and fibroglandular tissue volumes, and defined 100 spatially registered regions in each breast image. Association of breast morphology with breast cancer risk was measured using principal components of both absolute fibroglandular and percent fibroglandular volumes, and conditional logistic regression.

Results:
Breast tissue density morphology differed strongly between by cancer case/controls, normal/overweight, premenopause/postmenopause, and asian/white groups. Women who developed cancer were found to have higher local fibroglandular volumes in all breast mammogram locations with maximal differences in the outer lateral and central portion of the breast relative to those women without breast cancer.
The largest average difference of group distributions appears to be between the pre and postmenopausal groups. Risk models using principal components of breast density alone were found to be as predictive as models with risk factors alone.

Conclusion:
Spatial characteristics of breast density on a mammogram are strongly related to cancer risk and are strongly associated with a woman’s clinical risk factors. The results show that the cancer risk of dense tissue is determined by its position in the breast. Voxel-based morphometry is considered to provide additional information on association of breast cancer risk with regional breast morphology.

Title of Abstract: Masking and Breast Density – Can We Quantify Masking Risk?

Presenting Authors Full Name: Nico Karssemeijer

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Purpose: Fibroglandular tissue may mask breast cancers, thereby reducing the sensitivity of mammography. The purpose of this presentation is to present and review methods for identification of women at high masking risk based on mammographic images. These women could benefit from additional imaging.

Method: By retrospectively reviewing the last negative screening mammograms of women with interval cancer (IC) masking can be studied. Using mammograms with interval cancers, methods can be developed and evaluated that identify mammograms with density patterns associated with a high risk of masking cancers. Several methods are evaluated, including volumetric and area based density assesssment methods. Also model based techniques have been proposed, which involve mathematical techniques to determine detectability of lesions in structured backgrounds and probability maps representing the a priori spatial distribution of cancer locations.

Results: In a study involving 111 interval cancers it was found that existing volumetric measures of breast density perform reasonably well for the prediction of masking. More elaborate methods involving mathematical models are still under development.

Conclusion: Measures based on volumetric density maps are promising tools to identify women at high risk for a masked cancer.

Title of Abstract: Volumetric and BI-RADS Density Measures and Interval Cancers

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Purpose: To examine and compare quantitative volumetric breast density measures and BI-RADS density from digital mammography images with associated breast cancer outcomes including screen-detected and interval cancers according to time from breast density measure to cancer diagnosis.

Method: Participating studies included two retrospective case-control studies nested within large screening mammography practices, the Mayo Clinic Rochester (MCR) mammography practice and the San Francisco Mammography Registry (SFMR), for a total of 1615 screen-detected invasive cancers, 352 interval cancers, and 4445 controls matched on mammogram date, age, race/ethnicity, machine, and site. Both studies had clinical risk factors, BI-RADS density measures, and raw or “for processing” digital screening mammograms from Selenia-Hologic machines at least six months (average 3.0 years) prior to the cancer diagnosis (or corresponding date for controls). We measured volumetric percent density (VPD) and dense breast volume (DV) from the Volpara™ (version 1.5.3) programs. Invasive cancers were defined as screen-detected (invasive cancer within 12 months of positive screening examination) or interval cancer (invasive cancer within 12 months of negative screening examination). Breast cancer associations by type of detection were evaluated using conditional logistic regression, adjusting for age and body mass index. Odds ratios (OR), C-statistics (C) and 95% Confidence Intervals (CI) were estimated. Analyses were stratified by time from mammogram to diagnosis (<3 years, $\geq$3 years).

Results: BI-RADS breast density, DV and VPD measures were associated with both screened-detected and intervals cancers with significantly stronger associations with interval cancer (P-value <0.001). We will present how combinations of density measures and time from breast density measure to cancer diagnosis impact breast cancer associations according to mode of detection.

Conclusion: High dense volume or volumetric percent density or BI-RADS dense breasts increases women’s risk of a missed cancer. Risk models that estimate women’s cumulative risk of a missed cancer will need to consider which density measure(s) best predict future risk.

Poster Session #1

June 8, 2017

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Breast Density Clinical Guidelines, Reporting, and Supplemental Screening: Densebreast-info.org (DBI) as Modern Tool to Help Educate Women and Health Providers

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Purpose:
Purpose: Our purpose is to describe the development and expansion of Densebreast-info.org (DBI), a comprehensive, medically-sourced, and open access web-based information resource about breast density, supplemental screening, and patient notification legislation.

Method:
DBI is a nimble web-based resource created in collaboration by breast imaging experts and medical reviewers. Since its launch in April 2015, this free and flexible viewing tool educates patients, health providers, and the lay public on all topics pertaining to breast density and related breast imaging. The website also provides timely and accurate updates on breast density legislation and related efforts, at state and federal levels.

The website features 4 content tabs: For Patients, For Health Professionals, Screening Technologies and Legislation. The Patient and Health Professional tab content were developed with content and reader comprehension levels specific for each. Using Google Analytics, we calculated the total site visits (4/15- 2/17) and present data comparing the website's first 3 full months (5/1/15 – 7/31/15) to recent full 3 months (12/1/16-2/28/17).

Results:
As of end of February 2017, we have had nearly 70,000 site visits from at least 157 countries. Comparing first quarter 2017 to the initial 3 months in 2015, we have observed:

- 135% increase in numbers of website users (defined as initiating at least one session)
- 311% increase in page views (total # of pages viewed)
- 77% increase in # pages viewed per session
- 97% decrease in "bounce rate" (single page sessions)

Conclusion:
Clinical guidelines and reporting of breast density can be assisted with responsible tools that help women and providers become better informed. This medically sourced web resource is demonstrating encouraging engagement with increasing metrics, both within and outside of the USA.

Pubertal Timing Is Associated with Breast Composition 1 Year After Menarche Onset.

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Purpose:
Early menarche, thelarche and increased breast density(BD) are known risk factors for breast cancer; however, the relationship between pubertal timing and BD in adults is inconclusive. We have recently reported that Dual X-Ray Absorptiometry(DXA) is a valid method to measure BD in young women; thus our aim is to assess the relationship between pubertal timing and breast composition [absolute fibroglandular volume(AFGV) and % fibroglandular volume(%FGV)] in girls 1 year after menarche onset.

Method:
This study used the female participants(400) of the Growth and Obesity Chilean Cohort study born in 2002-2003. Biannual anthropometric and sexual maturation data was collected starting in 2009(6.5 y). We selected 100 girls 1 year post-menarche to measure DXA breast composition. DXA AFGV and %FGV of the breast derived considering a two-compartment model of adipose and fibro-glandular tissue using software developed by Shepherd at UCSF. Linear regression models, crude and adjusted by BMI at 1 year post-menarche and maternal age at menarche, were used to assess the relationship between pubertal timing(age at thelarche and menarche and time between both periods) with AFGV and %FGV at 1 year after menarche.

Results:
The age at thelarche was 8.9y(sd=1.1), age at menarche 11.1y(sd=0.5) and mean time between both markers 26 months(sd=12). The mean % FGV was 50.1%(sd=13.9) and AFGV 175.5 cm3 (sd=67.4). In the adjusted models, we observed that an earlier thelarche (ß=-3.3, 95%CI:-5.5;-1.1), and menarche(ß=-7.3, 95%CI:-12.2;-2.5) were associated with higher %FGV; a larger time between both markers was also associate with higher %FGV after further adjusting by age at menarche(ß=0.22, 95%CI:0.04;0.4). Higher AFGV was associated only with early thelarche and longer time interval between thelarche and menarche.

Conclusion:
Earlier pubertal timing is an important factor affecting breast composition 1 year after menarche; this has relevance in efforts to modify breast cancer risk in later ages.
(Funding WCRF2010/245, NCI/NIH:5R01CA158313 to K.B.M.)

Predicting Breast Cancer Risk Based on Information in a Mammogram Other Than Conventional Mammographic Density

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Purpose:
To predict breast cancer risk based on information in a mammogram by considering more than the conventional concept of mammographic density.

Method:
We conducted case-control or nested case control studies of Australian, Korean and/or Japanese women using analog or digital mammograms. First, we used the semi-automated CUMULUS software to measure mammographic density. We defined density conventionally as the 'white or bright' regions, and called these measures Cumulus. We then measured density at in effect higher pixel brightness thresholds by defining density as the 'bright', and then 'brightest', areas and called these measures Altocumulus and Cirrocumulus, respectively. Second, we used machine learning, image processing techniques, and Bayesian Lasso regression to combine 20 textural features not based on pixel brightness to create risk measures which we call Cirrus. The ability of measures to differentiate cases from controls on a population basis was assessed by the increase in odds per standard deviation of the risk measure adjusted for all potential confounders in the design or analysis (OPERA).

Results:
We consistently found that risk was better predicted by Altocumulus, Cirrocumulus and/or Cirrus than by Cumulus. The Cirrus measures learnt from one data set predicted risk almost as well on other data sets, even across Australian and Japanese women. The OPERAs for our new measures Altocumulus, Cirrocumulus and Cirrus were as high as 1.7, compared with OPERAs of 1.4-1.6 for the Cumulus measures. More importantly, when the different measures were estimated concurrently, the Cumulus measure reduced to the null.

Conclusion:
Conventional mammographic density is a surrogate for other mammography-based risk measures which give better discrimination than all currently known genetic and lifestyle risk factors. Combining mammography-based risk measures, especially with risk measures based on multi-generational family history and SNPs, could produce inter-quartile risk ratios of >10-fold. If automated, this could revolutionise breast screening.

Exploring the Prediction Performance for Breast Cancer Risk Using Mammographic Density at Higher Thresholds

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Purpose:
Percentage of mammographic dense tissue (PD), an important risk factor, is typically measured using thresholding where pixels whose values less than a threshold level was excluded. It has recently been suggested that increasing the conventional threshold value for area based PD in a semi-automatic visual assessment of mammograms may improve predictive ability. We investigated whether the approach might be applied to volumetric density using full field digital mammograms (FFDM).

Method:
Two case-control studies in a screening cohort from Manchester UK were used to examine this issue. There were 317 cases diagnosed at the time screening and 947 controls in the first study; and 318 cases diagnosed after the mammogram and 935 controls in the second study. Volpara was used to estimate volumetric density and dense tissue height (in mm) at each pixel using craniocaudal view mammograms. A range of threshold values, from 0mm (originally used by Volpara) to 25mm were examined. Prediction performance was assessed using Akaike information criterion (AIC).

Results:
Predictive ability, as expected, increases and then decreases with increases in thresholds in both studies. The best threshold value in terms of predictive ability found is 5mm, yielding a slightly lower AIC than the original PD by Volpara in both studies (ΔAIC=2.79 and 3.10 respectively). PD at 5mm added information to original Volpara PD in both studies, with $\Delta X2$=5.92 and 7.47 respectively. Further analysis of this multivariate model (PDs with threshold at 0 and 5mm together) has shown different dense tissues are associated with risk differently: percentage of those above 5mm is positively associated with risk; while those $\leq$ 5mm has an inverse association.

Conclusion:
Volumetric density using higher than conventional threshold value could improve risk prediction. The paper also reveals interesting relationship between risk and different dense tissues.

Relationship of Circulating Insulin-like Growth Factor Binding Protein-2 with Area and Volume Measures of Mammographic Density among Women Undergoing Image-Guided Diagnostic Breast Biopsy

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Purpose:
Mammographic density (MD) is a strong breast cancer risk factor that reflects the relative proportions of fibroglandular and adipose tissue, but its biologic underpinnings are poorly understood. Insulin-like growth factor binding protein-2 (IGFBP-2) is a promising, yet understudied, etiological marker that may be associated with MD, given its hypothesized dual effect on breast tissue: in vitro studies suggest that IGFBP-2 can promote cell proliferation as well as inhibit adipogenesis. We investigated associations of circulating levels of IGFBP-2 with both area (MD-A) and volume (MD-V) density measures in a cross-sectional study of women undergoing breast biopsy.

Method:
Serum IGFBP-2 was measured in duplicate using enzyme-linked immunosorbent assay in 296 women, ages 40-65, who underwent a diagnostic image-guided breast biopsy at University of Vermont affiliated centers. The inter- and intra-batch laboratory coefficients of variation for IGFBP-2 were <3%. MD-A and MD-V were assessed in craniocaudal views of the breast in digital mammograms using computerized thresholding software (cm2) and single X-ray absorptiometry (cm3). Relationships between IGFBP-2 levels and MD were assessed with Spearman's rank correlations (r). Spearman's partial rank correlations were estimated after removing the effects of age and body mass index (BMI).

Results:
Median (range) IGFBP-2 was 345.1 (90.0-938.6) ng/ml. IGFBP-2 was inversely correlated with BMI (r= -0.51, p<0.001) and was not associated with age (r= -0.0001, p=0.99). IGFBP-2 levels showed significant positive relationships with percent MD-A (r=

0.33, p<0.0001) and MD-V (r= 0.46, p<0.0001). After adjusting for age and BMI, these correlations were attenuated but remained statistically significant (rMD-A= 0.14, p=0.02; rMD-V= 0.28, p<0.0001).

Conclusion:
These results suggest positive correlations between serum IGFBP-2 levels and percent MD among women undergoing diagnostic breast biopsy. Ongoing efforts to study relationships between serum IGFs, their binding proteins, and MD measures may be valuable in understanding of the IGF-system in breast cancer etiology.

Texture Variation on a Mammogram and Risk of Breast Cancer

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Purpose:
To evaluate an automated measure V, the standard deviation of pixel intensity, from pre-diagnostic mammograms, in relation to breast cancer risk.

Method:
We examined the average V of the left and right breast images at two resolutions, 171um and 300um, among 974 breast cancer cases and 2193 matched controls in the Nurses' Health Studies. Initial models were adjusted for matching factors, including age, menopausal status, and hormone therapy use, while subsequent models additionally adjusted for percent mammographic density (PMD) measured with Cumulus.

Results:
V was modestly correlated with PMD (r=0.44-0.45, p<0.01). V was significantly positively associated with breast cancer risk, though was somewhat weaker for 300um (odds ratio (OR) per standard deviation (SD) increase=1.35, 95%CI: 1.24-1.46 and 1.30, 95%CI: 1.20-1.41 for resolutions 171um and 300um respectively). These associations were attenuated, but remained statistically significant after adjustment for PMD (OR per SD increase=1.23, 95%CI: 1.13-1.34 and 1.18, 95%CI: 1.09-1.29 for resolutions 171um and 300um respectively). Associations with V were similar for ER+ and ER- tumors (e.g., OR per SD increase171um=1.24, 95%CI: 1.13-1.37 for ER+ tumors and 1.27, 95%CI: 1.05-1.54, for ER- tumors, p-heterogeneity=0.82). Women in the highest tertile of PMD and the highest tertile of V had 3.19 times the risk of breast cancer compared to those in the lowest tertile of both measures (95%CI: 2.42-4.22 for 171um). In a preliminary analysis, we examined the difference in V between the left and right breast images. Higher differences in V were associated with subsequent breast cancer risk (OR per SD increase171um=1.12, 95%CI: 1.04-1.21); this association was somewhat attenuated after adjustment for PMD (OR per SD increase171um=1.07, 95%CI: 0.99-1.16).

Conclusion:
Higher levels of V were associated with greater risk of breast cancer independent of PMD. Future work will examine other measures of texture.

A case-control study to assess the ability of BIRADS and volumetric density to refine Tyrer-Cuzick model breast cancer risk predictions

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Purpose:
To evaluate the ability of visual or volumetric mammographic density to refine Tyrer-Cuzick model breast cancer risk assessment.

Method:
A case-control study (480 cases and 2299 controls) of women aged 40-79 years was performed using self-reported classical risk factors from women in Virginia, USA. Breast density was measured using automated volumetric software (Volpara) and BI-RADS categories. Odds ratios (95% CI) were estimated by logistic regression, adjusted for age and demographic factors and 10-yr risk from the TC model. Observed risk from volumetric density was compared with BI-RADS categories by frequency matching in controls.

Results:
After adjustment for the Tyrer-Cuzick model, the odds ratio for the dense vs fatty BI-RADS category was 2.80 (95%CI 1.75-4.47, LR-χ2 28.4) compared with 2.37 (95%CI 1.50-3.73, LR-χ2 22.3, P=0.22) for equivalent volumetric density categories. Absolute fibroglandular volume was a weaker predictor (LR-χ2 11.3) than BI-RADS (P=0.03) or volumetric percent density (P=0.07). When the TC model was combined with volumetric density using these risks, we estimated that in similar populations it may identify a high-risk group containing 43% of all breast cancers in 22% of the women, and a low-risk group with 8% of the cancers in 20% of the women.

Conclusion:
Volumetric and visual density measures add useful information to risk models.

Is Change in Mammographic Density after Breast Cancer Treatment Associated with Outcomes?

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Purpose:
Mammographic density (MD) is one of the strongest known risk factors for breast cancer incidence, but its role in disease progression is less clear. Preliminary studies suggest that a reduction in MD following tamoxifen predicts treatment response, but data are limited and somewhat inconsistent.

Method:
We evaluated associations of changes in percent density (PD) and dense area (DA) with risk of second breast cancer events using a case-cohort study of 931 patients from the Life After Cancer Epidemiology (LACE) and Pathways cohorts. MD was measured on digitized film mammograms by a trained reader using Cumulus, and change in MD was defined as the absolute difference between PD or DA at diagnosis and two years post-diagnosis. Second breast cancer events were defined as recurrence, contralateral breast cancer, or breast cancer-specific death. We used Cox proportional hazards models modified for the case-cohort design to calculate relative risks and 95% confidence intervals (95% CI).

Results:
Roughly two-fifths of women maintained stable MD between diagnosis and two years post-diagnosis (-2.4% ≤ ∆PD ≤ 2.4%: 44%; -2.4cm2 ≤ ∆DA ≤ 2.4cm2: 38%). Relative to such women, those who lost ≥10% PD were not at an increased risk of a second breast cancer event (multivariable RR: 1.06; 95% CI: 0.59-1.93). Results for a loss of DA ≥10cm2 were similarly null (RR: 1.07; 95% CI: 0.62-1.83). Average reduction in density was greatest for women treated with tamoxifen, but analyses restricted to this subgroup showed no material changes in results.

Conclusion:
Our results do not support the limited existing evidence suggesting that reductions in MD following breast cancer diagnosis and treatment are beneficial.

LIBRA: The Laboratory for Individualized Breast Radiodensity Assessment

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Purpose:
The amount of fibroglandular tissue in the breast as estimated mammographically, commonly referred to as percent density (PD%), is one of the most widely established risk factors for breast cancer. We present an update for the publicly-available software package, the Laboratory for Individualized Breast Radiodensity Assessment (LIBRA), which allows for fully-automated breast density estimation from digital mammography images.

Method:
Briefly, the LIBRA software first applies an edge-detection algorithm to delineate the boundary of the breast and the boundary of the pectoral muscle. Following the segmentation of the breast, an adaptive multi-class fuzzy c-means algorithm is applied to identify and partition the mammographic breast tissue area into multiple regions of similar x-ray attenuation. These clusters are then aggregated by a support-vector machine classifier into a final dense tissue area segmentation. The ratio of the segmented absolute dense area to the total breast area is then used to obtain a measure of breast percent density (PD%). LIBRA also generates the corresponding breast and dense tissue area segmentations overlaid on the original mammographic image.

Results:
LIBRA has been validated against the widely used semi-automated Cumulus method and BIRADS density estimates, showing high agreement ($r=0.85$-0.89, $k=0.62$-0.64, $p<0.001$). LIBRA has been successfully applied to more than 50,000 mammography screening exams and is increasingly utilized by the research community. We will review on-going studies validating LIBRA in breast cancer risk assessment and its most recent software extensions for synthetic 2D mammograms and volumetric density estimation from 3D digital breast tomosynthesis.

Conclusion:
LIBRA is publically available as open-source software that can be used freely for research purposes (http://www.cbica.upenn.edu/sbia/software/LIBRA/index.html). Given the increasing interest in automating density assessment, and its applicability to both digital mammograms and breast tomosynthesis images, LIBRA could pave the way for larger studies evaluating automated breast density measures in breast cancer risk assessment.

Intraindividual Variation in Breast Composition: Implications for Studies of Normal Breast Histology

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Purpose:
To understand the effects of intraindividual variability of breast composition on measures of age-related involution and apply this knowledge when studying risk factors for age-related involution.

Method:
A measure of age-related epithelial involution (density of epithelial nuclei in epithelial areas) was assessed by digital image analysis, along with stromal characteristics (percentage of section area comprised of stroma). Approximately 1,800 hematoxylin and eosin stained sections of benign breast tissue were evaluated from 416 participants having breast surgery for cancer or benign conditions. At least two and up to sixteen slides per woman, from different regions of the breast, were included.

Results:
Epithelial content varied within a woman and as a function of stromal area. Percentage stromal area varied between samples from the same woman (median difference between highest and lowest stromal area within a woman was 7.5%, but ranged from 0.01-86.7%). Restricting to women with at least 10% stromal area (N=317), epithelial nuclear density decreased with age (-637.1 cells/mm2 per decade of life after age 40, $p<0.0001$), increased with mammographic density (457.8 cells/mm2 per increasing BI-RADs density category $p=0.002$), and increased non-significantly with recent parity, later age at first pregnancy, and longer and more recent oral contraceptive use. These associations were attenuated in women with mostly fat samples [<10% stroma (N=99)]. 30.6% of women evaluated had both adequate stroma (≥10%) and mostly fat (<10% stroma) regions of breast tissue, with the probability of having both types increasing with the number breast tissue samplings.

Conclusion:
Stratification on stromal content yields distinct associations between breast cancer risk factors and age-related involution, with patterns being more evident in samples coming from areas of high local density. The cutpoint identified (10% stroma) represents a potential method by which to pinpoint histological samples that may be more informative for breast cancer histology studies.

Breast Cancer Risk Assessment Using Two Existing Models in Women with Extremely Dense Breasts Participating in a Trial on Supplemental Breast Cancer Screening with MRI

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Purpose:
It has been suggested that besides breast density, estimated 5-year breast cancer risk should also be considered when deciding for supplemental imaging. We estimate breast cancer risk, using existing risk prediction models, in women with extremely dense breasts who participate in a trial on supplemental breast cancer screening with MRI (DENSE).

Method:
We used the Breast Cancer Surveillance Consortium-Benign Breast Disease (BCSC-BDD) model and a modified Gail model (including density) to calculate 5-year breast cancer risk for women with extremely dense breasts participating in the DENSE trial. Gail risks were not calculated when information on ≥1 risk factors was missing. Risk estimates ≥1.67% were considered as increased 5-year risk. Differences in estimates between the models were assessed.

Results:
In a group of, 4,783 participants (median age 54, IQR:51-59), who all had extremely dense breasts, BCSC-BDD risk was increased for 71.2%, and Gail risk for 97.4%. For women in whom both risks could be calculated, we found that in 98.8% (2,584/2,614) of the women with an increased BCSC-BDD risk, Gail risk was also increased. In only 5.9% (66/1,128) of the women with normal BCSC-BDD risk, however, the Gail risk was also normal. When we examined, independent of the actual scores, the ranking of the women in their risk score distributions, 86.7% of women in the highest 71% of BCSC-BDD risks (‘increased risk’) were also in the highest 71% of Gail risks, 63.2% of women in the lowest 29% of BCSC-BDD risks were also in the lowest 29% of Gail risks.

Conclusion:
Both models predicted an increased 5-year risk for the majority of the participants with extremely dense breasts (71-97%). After adjusting for differences in the scales, the Gail risk estimates show moderate agreement with BCSC-BDD risks. The identification of women with an increased risk thus depends on the model that is used.

Personalized Risk Assessment in a Population-Based Trial: WISDOM Trial in Progress

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Purpose:
Women Informed to Screen Depending on Measures of risk (WISDOM) trial is a pragmatic study comparing two real world approaches to clinical care for breast screening: annual screening versus personalized screening. The novelty of the personalized arm of the study is that we are combining known risk factors, age, family history, history of breast disease, ethnicity, BIRADS breast density, and genetics into a single risk assessment model. The goal of the WISDOM study is to examine the effectiveness of personalized breast cancer screening and to bring objective recommendations to the current mammography screening debate.

Method:
The WISDOM trial will enroll 100,000 women at University of California Medical Centers and Sanford Health with a preference-tolerant design that will determine if risk-based screening vs. annual screening, is as safe, less morbid, enables prevention, and is preferred by women. For all participants, 5-year risk of developing breast cancer is calculated according to the Breast Cancer Screening Consortium (BCSC) model. For participants in the personalized arm, the overall 5-year risk BCSC score is combined with a Polygenic Risk Score, based on a panel of single nucleotide polymorphisms known to modify breast cancer risk. Risk thresholds will determine frequency of screening. The study is registered on ClinicalTrials.gov as NCT02620852. The study is supported by the Patient-Centered Outcomes Research Institute (PCORI), PCS-1402-10749.

Results:
The WISDOM trial is currently open for recruitment at UCSF and UCSD. As of March 24, 2017, we have invited 29,151 eligible women at both sites. 1,992 have consented in the trial. 65% were randomized and 35% chose their screening arm. A pilot was conducted to test the logistics of online participation and examine the acceptance of the study design and approach.

Conclusion:
Enrollment will be completed by the end of 2018.

A Pilot Study of Shear Wave Elastography and High Mammographic Breast Density (HMBD) in Women Undergoing Testosterone/Anastrozole Therapy for Breast Density Reduction

Presenting Authors Full Name: Stephen N Birrell, MD, PhD

Institution: Havah Therapeutics

Additional Author's Names as to be Published: none

Purpose:
Breast stiffness or elasticity is directly related to mammographic breast density (MBD) (1) and therefore the risk of developing breast cancer. To date elasticity could only be estimated but now Supersonic Aixplorer® shear wave ultrasound allows for direct measurement of breast elasticity.

(1) Boyd NF et al Evidence That Breast Tissue Stiffness Is Associated with Risk of Breast Cancer. PLOS July 2014 9 (7)

Method:
Ten pre-menopausal women (median age 41yrs (36-48) currently menstruating with gonadotropins in the normal range) with HMBD (>15.5 % MBD as measured by Volpara) and with measureable mastalgia received a combination of T 80mg and an AI (anastrozole) 2mg combined in a subcutaneous implant (inserted in the lower abdominal or gluteal subcutaneous fat). Breast elasticity and pain scale were measured at baseline and 6 weeks.

Results:
Ten women commenced and completed the study.
Baseline %MBD = 20.26 (4.1)
Baseline kPa = 82.48 (14.7)
6-week kPa = 38.71 (14.3)
Baseline VAS = 46.6 (17.7)
6-week VAS = 15.6 (9.9)

kPA=kilopascals (Young's Modulus)
VAS = 100mm visual analogue score for the worst pain experienced in the 6 weeks prior to treatment and at the end of treatment.
Results shown as mean (+/- SD).

Conclusion:
Shear Wave elastrography with Supersonic Aixplorer® ultrasound is a simple and non-invasive way of calculating breast tissue response to a hormonal therapeutic intervention for MBD.

Title of Abstract: Quantitative imaging phenotyping of breast cancer risk

Presenting Author's Full Name: Aimilia Gastounioti

Institution: University of Pennsylvania

Additional Author's Names as to be Published: Andrew Oustimov, Meng-Kang Hsieh, Lauren Pantalone, Eric Cohen, Stacey Winham, Dana H. Whaley, Carrie B. Hruska, Karla Kerlikowske, Kathleen Brandt, Celine Vachon, Emily F. Conant, Despina Kontos

Purpose: To elucidate the emerging role of parenchymal complexity analysis as a potential novel approach to complement breast density toward augmenting quantitative imaging phenotyping of breast cancer risk.

Method: Using state-of-the-art automated tools for parenchymal texture analysis, we compared parenchymal complexity measurements extracted from the two types of images (raw versus processed mammograms) generated from digital mammography, where potential interactions with woman- and system-specific factors were also assessed. We also evaluated whether incorporating breast anatomy information could strengthen the associations of quantitative parenchymal complexity measures with breast cancer risk. Moreover, we used unsupervised clustering to identify intrinsic phenotypes of breast parenchymal complexity and we investigated their implications for mammographic density assessment.

Results: Differences in measures from processed versus raw digital mammograms vary substantially across features, vendors and image acquisition settings, where structural features appear to be more robust. Incorporating anatomic variables in breast parenchymal texture analysis results in higher case-control discriminatory capacity than methods that do not consider breast anatomy, with the potential to also improve personalized breast cancer risk assessment. Also, unsupervised clustering of quantitative parenchymal complexity features extracted from screening digital mammograms revealed distinct intrinsic phenotypes of increasing breast complexity, which do not correlate with breast density.

Conclusion: Automated breast parenchymal complexity measures based on texture analysis have the potential to provide novel imaging phenotypes of breast cancer risk, which may be valuable for personalizing routine breast cancer screening and prevention strategies. Future work involving large prospective studies, new technologies (e.g., deep learning) and emerging modalities (e.g., breast tomosynthesis) are expected to further enhance and establish the predictive value of quantitative breast imaging phenotypes.

An Open Labelled Evaluation of Subcutaneous Combined Testosterone / Anastrozole Implants in Pre-Menopausal Women with High Volumetric Mammographic Breast Density (HMBD).

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Institution:
Havah Therapeutics

Additional Author's Names as to be Published:
Nicholas D Birrell, BSc, MSc, PhD

Purpose:
This observational study examines a novel therapy that intends to alter the intra-mammary ratio of estrogen to testosterone to reduce HMBD in pre-menopausal women without perturbations in hypothalamic-pituitary function.

Tamoxifen therapy as a preventative agent for breast cancer has limited success in pre-menopausal women due, in part at least, to its significant side-effects. In pre-menopausal women, tamoxifen has an adverse effect on hypothalamic-pituitary function resulting in hyper-stimulation of ovarian function. Much of estrogenic effect in HMDB tissue results from intense aromatase activity converting testosterone to estrogen, whereas when testosterone is reduced to di-hydrotestosterone there is a profound reduction in estrogenic action on normal breast tissue.

Method:
150 women undergoing mammographic screening with HMBD >15.5% volumetric breast density (%VBD) as measured by Volpara® were allocated in a 1:1 non-randomised fashion to either (a) follow-up mammography at 1-year (b) treatment with a subcutaneous implant containing testosterone 80 mg and anastrozole 2 mg every 4 months plus a follow-up mammogram at 1 year.

Primary endpoints were %VBD after one year of therapy and impact on hypothalamic-pituitary function.

Results:
None were lost to follow-up during the study period. There was a relative reduction in MBD of 2% v's 19.5% (controls v's treatment arm), no significant change in either FSH or LH, no serious adverse events and no androgenicity events resulting in cessation of treatment.

Conclusion:
Testosterone/anastrozole implants reduced HMBD in pre-menopausal women with excellent tolerance and no adverse effect on hypothalamic-pituitary function.

Title of Abstract: **Microcalcifications, Masses, Density, BMI, HRT, and Family History of Breast Cancer Used to Create a 2-Year Risk Model for Use in Individualized Screening**

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Institution: Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden

Additional Author's Names as to be Published: Kamila Czene, Yudi Pawitan, Karin Leifland, Hatef Darabi, Per Hall

Purpose: The individual risk needs to be assessed to efficiently screen for breast cancer. We describe a model that stratify women's risk and could be used at most mammography screening units without adding substantial cost.

Method: The study was based on the KARMA cohort including 70,877 participants. Mammograms were collected up to three years following baseline mammogram. A prediction protocol was developed using mammographic density, computer-aided-detected microcalcifications and masses, use of hormone replacement therapy (HRT), family history of breast cancer, menopausal status, age, and body mass index. Relative risks were calculated using conditional logistic regression. 2-year absolute risks were calculated.

Results: Comparing women at highest and lowest mammographic density yielded a 5-fold higher risk of breast cancer for women at highest density. When adding microcalcifications and masses to the model, high-risk women had a nearly 9-fold higher risk of breast cancer compared to those at lowest risk. In the full model, taking HRT use, family history of breast cancer and menopausal status into consideration, area under the curve (AUC) reached 0.71.

Conclusion: Measures of mammographic features and information on HRT use, family history of breast cancer and menopausal status enabled early identification of women within the mammography screening program at such a high risk of breast cancer that additional examinations are warranted. In contrast, women at low risk could probably be screened less intensively.

Rapid Reductions in Breast Density Following Tamoxifen Therapy as Evaluated by Whole Breast Ultrasound Tomography

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Purpose:
Data indicate that women whose mammographic breast density (MBD) declines within 12-18 months after tamoxifen for chemoprevention or adjuvant treatment are more likely to respond clinically than those whose MBD does not decline. Thus, defining more rapid and accurate means for identifying declines in density may have value for predicting treatment effectiveness.

Method:
In the Ultrasound Study of Tamoxifen, we used a novel 3D whole breast ultrasound tomography (UST) method to assess change in sound speed, a surrogate of volumetric breast density, at 1-3, 4-6, and 12 months following start of clinically-indicated tamoxifen use among 74 women (aged 30-70 years) enrolled at Karmanos Cancer Institute and Henry Ford Health Systems (Detroit, MI) between 2011-2014. UST measurements at baseline and 12 months were compared with 150 women with negative mammographic screening results matched on age, race, and menopausal status. Serum was collected at baseline and 12 months.

Results:
At the 12-month follow-up, sound speed was significantly reduced in the tamoxifen group (mean (SD): -3.0 (8.2) m/s; P=0.001) but remained relatively stable in the comparison group (mean (SD): 0.4 (7.1) m/s; P=0.75), and this difference between groups was statistically significant (P=0.0009). Among the tamoxifen group, we identified continuous declines in breast density, with significant sound speed reductions observed as early as 4-6 months after tamoxifen initiation (mean (SD): -2.1 (6.8) m/s; P=0.008). Sound speed reductions were greatest among patients in the middle and upper tertiles of baseline sound speed (P-interaction=0.008).

Conclusion:
UST may have utility in sensitively assessing early breast density changes. Analyses are ongoing to identify whether circulating growth factors and tamoxifen metabolites are associated with sound speed change in these participants in an effort to understand biologic correlates of sound speed change.

Mandatory Breast Density Reporting in Massachusetts: Patient Understanding and Effects on Screening Intentions

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Purpose:
Massachusetts became the 18th state to pass legislation requiring patient notification about dense breast tissue. The law went into effect on January 1, 2015. Our goal was to assess women's beliefs and knowledge about breast density, interactions with health professionals regarding breast density, and the effect of notification on intentions for future screening.

Method:
We conducted semi-structured interviews with 20 female participants of the Boston Mammography Cohort Study, a cohort of women receiving routine screening mammograms at Brigham and Women's Hospital in Boston, MA. Interview eligibility criteria included: a screening mammogram after 12/31/2014, no personal history of breast cancer, and measured volumetric breast density in the highest category of Volpara density grade (comparable to BIRADS=4).

Results:
Participant mean age was 64.4 years. 75% were non-Hispanic white, with the remaining participants non-Hispanic Black. Most participants defined density as something related to breast fatness or thickness and thought it might make it harder to find breast cancer. However, the majority expressed doubt about their definition, with many stating that they were unsure or guessing. Most women said they had not or could not recall discussing breast density with a healthcare provider. Though all 20 interviewed women had dense breasts, just eleven (55%) recalled receiving written notification. Many had heard of additional breast screening options such as MRI or ultrasound because they had been recommended or had received one of the additional screenings. All participants would at least consider additional screening options if .they had an issue or a problem or their doctor recommended it.

Conclusion:
Women expressed confusion about breast density, but were aware of a relationship to mammogram performance, and the possibility of using other screening modalities. Most had not discussed breast density with their doctors, and felt that their doctor's advice was central to their future screening decision-making

Breast Cancer Risk Assessment

Putting it all together

June 9, 2017

Involution and Breast Density

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Mayo Clinic

Purpose: Elevated mammographic density is associated with increased risk of developing breast cancer, but the mechanisms that mediate this association are undefined. Possible mediating factors include: increased at-risk epithelium and epithelial-stromal interactions. Density may also represent a biosensor of systemic effects related to risk. This presentation will explore associations between mammographic density and involution of terminal duct lobular units (TDLUs) of the breast, which represent the structures from which most breast cancer precursors arise. The goal is to highlight critical unanswered questions that may have translational implications for risk assessment and prevention.

Method: Presentation will focus on data from studies that describe factors that influence TDLU involution among healthy participants in the Komen Tissue Bank and understanding associations between density and histologic / pathologic features among women biopsied for clinical indications in the National Cancer Institute Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project.

Results: Mammographic density and TDLU involution are correlated, with somewhat variable associations depending on population and methods of assessment. However, data from the Mayo Benign Breast Disease cohort suggest that these factors contribute additively to predict breast cancer risk.

Conclusion: Refining knowledge of the associations between mammographic density and TDLU involution may enable refined risk assessment and foster insights into mechanisms that hasten involution, suggesting approaches to lower risk. However, many unanswered questions about the relationships of density and TDLU involution remain and new technologies may help address these unknowns.

Using Convolutional Neural Networks to Delineate Pathological Correlates of Mammographic Breast Density from Diagnostic Image-Guided Breast Biopsies

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Purpose:
Mammographic density (MD) is a strong breast cancer risk factor that reflects the fibroglandular composition, but specific tissue features associated with density are incompletely characterized. We hypothesize that convolutional neural network (CNN) analysis of breast tissue sections (deep learning) may enable identification of specific histologic features that underpin the increased breast cancer risk associated with high MD.

Method:
H&E stained tissue sections of diagnostic image-guided breast biopsies were evaluated among 588 women enrolled in the Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project (2007-2010). A CNN model was trained to identify and quantitatively assess breast stroma, epithelial and adipose tissue. Least absolute shrinkage and selection operator (Lasso) regression determined relationships between histological features and overall volumetric and localized MD measures. A cross-validation strategy assessed performance of the fitted model. Spearman correlation coefficients were estimated to test associations between predicted density (overall or localized MD) and actual MD measurements. We report the average (standard deviation) of these correlation coefficients.

Results:
In an independent validation set, the CNN model was 95.5% accurate in classifying epithelial, stromal and adipose tissue. Mean (SD) correlations between predicted and actual measurements for overall and localized MD were 0.70 (0.06) and 0.65 (0.06). Normalized stroma amount had the highest selection probability (Lasso P-score) and strongest positive relationship with MD (P-score>0.9 for each MD measurement). No association was observed for normalized epithelial tissue amount or the total normalized adipose area with MD. Number of epithelial regions was positively associated, whereas the distance between regions was inversely associated with overall MD (P-score<0.87 and 0.62, respectively).

Conclusion:
CNN analysis found that elevated MD was associated with greater stromal tissue amount and spatial distribution patterns of epithelial regions. CNN modeling to determine features that distinguish benign from malignant tissue in high vs. low MD is ongoing.

Large Breast Cancers in Women Attending Regular Screening: Risk Factors and Implications for Prognosis

Presenting Authors Full Name: Fredrik Strand, MD MSc

Institution: Karolinska Institute, Stockholm, Sweden

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Purpose:
Ever since breast cancer screening was introduced there has been a debate about its utility. A recent study focused on the persisting high incidence of large tumors despite the introduction of population-based screening programs. In this study, we aim to risk factors directly associated with tumors not being detected until larger than 2 cm, and to examine how this relates to long-term prognosis.

Method:
We examined a population-based screening cohort of 2,358 cases of invasive breast cancer incident between 2001 and 2008. The main outcome was a tumor size larger than 2 cm, compared to smaller. Multiple adjusted odds ratios for the association between percent density (PD), body mass index (BMI) and other patient characteristics and the main outcome were estimated. We followed the patients until 2016, and estimated age-adjusted hazard ratios for disease progression – defined as the first of locoregional relapse, distant metastasis or death due to breast cancer. All analyses were stratified by detection mode.

Results:
For screen-detected cancers, both BMI (Odds Ratio (OR): 1.33 per 5 kg/m2) and PD (OR: 1.26 per 10%PD) were associated with having a large tumor at diagnosis. However, for interval cancers, only BMI (OR: 1.56) was associated with having a large tumor, while PD (OR 0.81) was associated with having a small tumor. Nulliparity was only significant among screen-detected cases (OR 1.45). Large tumors were associated with worse prognosis than smaller ones (Hazard Ratio (HR): 2.66). Women with higher BMI had worse prognosis than women with lower BMI (HR 2.01) – among interval cancers only. PD showed no significant association with disease progression.

Conclusion:
In light of our findings, efforts to improve breast cancer screening by finding tumors while they are still small, should primarily focus on shortening the time interval between screenings for women with high BMI.

Micro-structure and micro-mechanics of breast density

Michael Sherratt

NOTES

Title of Abstract: iCARE Breast Cancer Risk Model Development and Validation

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Additional Author's Names as to be Published: Parichoy Pal Choudhury, Amber Wilcox, Mark N. Brook, Thomas Ahearn, Nick Orr, Minouk Schoemaker, Michael Jones, Anthony Swerdlow, Nilanjan Chatterjee

Purpose: To develop and validate breast cancer risk models using a flexible approach to integrate information on known risk factors and polygenic risk scores (PRS).

Method: We have developed a synthetic risk modelling approach (iCARE) for breast cancer based on estimates of risk factor relative risks (RR) reported in the literature and PRS from the Breast Cancer Association Consortium (BCAC). The current model includes the following risk factors: age at menarche, parity, age at first birth, oral contraceptive use, age at menopause, menopausal hormone therapy, body mass index, height, alcohol intake, benign breast disease and family history of breast cancer. Population-based information on risk factor frequencies, incidence and mortality rates were used to obtain estimates of absolute risk. Model performance for 5-year absolute risk predictions in women 50 years or older was assessed in a prospective cohort studies in the UK (Breakthrough Generations Study, BGS: 36,921 women, 621 cases). Assigned and observed risks for different risk categories were compared using the Hosmer-Lemeshow (HL) statistic to assess model calibration. The area under the receiver operator curve (AUC) was calculated to assess model discrimination.

Results: For a model including only non-genetic risk factors, the relative risk score and projected 5-year absolute risk were well calibrated (P=0.72 and P=0.25, respectively) and the AUC was 0.60 (95% CI 0.58-0.62). In contrast, the AUC for a PRS based on 93 single nucleotide polymorphisms (SNPs) is 0.62. Integration of risk factor and the 92-SNP PRS results in further risk stratification (AUC=0.65). This level of risk discrimination can be further improved with the addition of novel SNPs identified in the OncoArray project (ongoing analyses).

Conclusion:
We have developed a flexible modelling approach that uses information on risk factor relative risks from the literature that is well calibrated in a UK population. This model can be easily expanded to include PRSs, as well as additional factors such as mammographic breast density to build comprehensive risk models.

Poster Session #2

June 9, 2017

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Design of a Case-Cohort Study to Address Gaps in Knowledge About Mammographic Density and Breast Cancer Risk in African American Women

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Purpose:
Despite recognition as one of the strongest predictors of breast cancer in populations of European ancestry, high mammographic density (MD) is not an established risk factor in African American women, nor are there any risk prediction models specific to African American women that incorporate MD. Racial differences in the MD-breast cancer association could contribute to racial disparities in breast cancer subtypes.

Method:
To address significant gaps in knowledge about the relation of MD to breast cancer risk in African American women, we will establish a mammogram repository within the Black Women's Health Study, an ongoing prospective cohort of 59,000 African American women with over 20 years of epidemiological and clinical data. We are planning a case-cohort study to retrieve multiple screening (pre-diagnostic) full-field digital mammogram images from approximately 6700 women, including at least 700 incident breast cancer cases. We will measure absolute and percent MD using Cumulus and estimate the risk of breast cancer, overall and by ER status, associated with high MD in this understudied population. We will also assess the relation of known and suspected breast cancer risk factors to measures of MD.

Results:
We submitted an R01 grant application to conduct this research and received a fundable score; we expect to begin this project in July. This resource will constitute the largest screening mammogram repository among African American women with individual-level risk factor information spanning many years.

Conclusion:
The overall impact of this research will be to provide etiologic insights on the relation of MD to breast cancer risk, overall and by subtype, in African American women. Findings from this study will also be used to build better risk prediction models for African American women to identify those at highest risk for targeted interventions and risk reduction strategies.

Acknowledgments: We are grateful to Rulla M. Tamimi and Martin J. Yaffe for their advice and guidance in designing this study. The Black Women's Health Study is supported by the NCI (grants CA058420, CA164974).

A Novel and Fully Automated Breast Cancer Risk Measurement Based on Digital Mammographic Texture: Evidence from Two Case-Control Studies

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Purpose:
The percentage of mammographic dense tissue (PD) is an important risk factor for breast cancer, and there is some evidence that texture features may further improve predictive ability. However, relatively little work has assessed or validated textural feature algorithms using raw full field digital mammograms (FFDM), which this paper seeks to examine.

Method:
A case-control study nested within a screening cohort (age 46-73y) from Manchester UK was used to develop a texture feature risk score (264 cases diagnosed at the same time as mammogram of contralateral breast, 787 controls) using the least absolute shrinkage and selection operator (LASSO) method, and validated in a second case-control study from the same cohort but with cases diagnosed after the index mammogram (317 cases, 931 controls). Predictive ability was assessed using Akaike information criterion (AIC) and matched concordance index (mC). The ability to refine risk estimation beyond percent volumetric density (Volpara) was tested using conditional logistic regression.

Results:
The strongest features identified in the training study were “Sum Average” based on the grey-level co-occurrence matrix at low image resolutions (original resolution 10.628 pixels per mm; downsized by a factor of 16, 32 and 64), which had lower AIC and higher mC than Volpara PD. In the validation study, the risk score achieved a better AIC than PD (ΔAIC=10.55) as well as a similar mC to PD (0.58 and 0.57 respectively). The risk score added independent information to PD ($\Delta\chi 2 = 14.38$, $p = 0.0008$).

Conclusion:
Textural features based on digital mammographic improve risk assessment based on volumetric density. The features and risk score developed needs further investigation in other settings.

Mammographic Density as a Predictor of Breast Cancer Risk and Mortality in Western Australian Aboriginal Women3/24/2017

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Purpose:
The distribution of mammographic density (MD) in Australian Aboriginal and Torres Strait Islander (ATSI) women and its association with breast cancer (BC) risk and mortality is unknown. We've conducted a retrospective screening-population case-control study to investigate associations between MD and BC risk and mortality in ATSI and non-ATSI women.

Method:
We obtained mammographic images from every ATSI women diagnosed with BC via Western Australia's BreastScreen program since 1994 and age- and location-matched controls: 119 ATSI cases, 937 ATSI controls, 355 non-ATSI cases and 1030 non-ATSI controls. Of these, 214 have died from the disease. Cumulus measurement is underway and complete for 825 women (85 ATSI cases, 233 ATSI controls, 249 non-ATSI cases, 258 non-ATSI controls). Logistic regression and survival analysis will be used to examine the association between MD measures and BC risk and mortality adjusted for age, ATSI status, hormone therapy use, family history, and indicators of geographic remoteness and socio-economic disadvantage.

Results:
The complete analysis will be available by the time of the meeting. Preliminary analyses show that the median percent density and interquartile range for ATSI and non-ATSI controls is 3% (1%-15%) and 14% (3%-26%), respectively. Unadjusted mean percent density is higher in cases than controls for both groups and significantly lower in ATSI women compared to non-ATSI women. Means for ATSI cases and controls are 12.2% (SD=13.0) and 10.1% (SD=14.2) and for non-ATSI cases and controls are 19.0 (SD=16.8) and 17.3% (SD=16.4), respectively.

Conclusion:
Improving BC screening and outcomes for Western Australian Aboriginal women is a priority for BreastScreen WA and this research will fill significant gaps in knowledge regarding predictors of BC risk and mortality in Aboriginal women. In particular, these analyses may identify or exclude potential risk factors to help explain why ATSI women are twice as likely to die from BC compared to non-ATSI women.

An Evaluation of Densitas, a Mammographic Density Method for Processed Images

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Purpose:
Breast density is a significant risk factor for breast cancer. A number of automated methods have been developed to assess breast density with varying predictive ability for breast cancer risk. Here we assess Densitas, a new automated area-based method using processed (for presentation) images for calculating breast density, and examine the risk of developing breast cancer.

Method:
Women were recruited to the Predicting Risk Of Cancer At Screening (PROCAS) study in Greater Manchester. Mammographic density on entry to PROCAS was assessed using Densitas which utilises the processed digital images and provides an area-based measure of dense area (DA), percent breast density (PD) and breast density grades based on BIRADS-4 or BIRADS-5. Women without breast cancer had two sequential cancer free mammograms. Odds ratios (OR) for quintiles of breast density and the risk of breast cancer were estimated using logistic regression after adjusting for classical risk factors.

Results:
A total of 958 cancers and 33520 non-cancers were eligible for the study. Compared to lowest quintiles of PD and DA those in the highest quintiles had significantly increased odds of developing breast cancer (OR 1.88, 95%CI: 1.52-2.32 and 1.68, 95%CI: 1.35-2.08 respectively). This relationship was increased further for PD (OR 2.29, 95%CI: 1.79-2.94), but not for DA (OR 1.72, 95%CI: 1.37-2.17) after adjustment, and appeared to be stronger for interval (PD OR 4.35, 95%CI: 2.56-7.41) than screen detected cancers (PD OR 1.95, 95%CI: 1.21-2.09). Only 10 women (all non-cancers) were categorised in the top category (4) for BIRADS-4 but the adjusted odds ratio for BIRADS-5 category D (30 cancers, 927 non-cancers) was significantly increased compared to category A (OR 2.02, 95%CI: 1.26-3.24).

Conclusion:
Densitas may be useful in predicting the risk of developing breast cancer, and as a practical method for risk stratification, particularly where raw image data are unavailable.

Histologic Correlates of Background Parenchymal Uptake on Molecular Breast Imaging

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Purpose:
Background parenchymal uptake (BPU) on molecular breast imaging (MBI), which describes the level of Tc-99m sestamibi uptake in fibroglandular tissue, varies among women with similar mammographic density and is independently associated with breast cancer risk (OR of 3.4 – 4.8 for high v. low BPU). We investigated histologic correlates of BPU that may explain this association.

Method:
Healthy female volunteers with a region of mammographically-dense tissue amenable to biopsy that also exhibited one of the extreme BPU categories – marked or photopenic – on MBI were recruited. Ultrasound-guided core-needle biopsies were performed by a radiologist. Tissue composition, estrogen-receptor-alpha expression, and Ki-67 expression were quantitatively measured on specimens using Aperio software. Lobular involution was assessed by an expert pathologist into 3 categories (none, partial, complete).

Results:
Of 48 participants, 28 had photopenic and 20 had marked BPU on MBI. Subjects with marked BPU were younger (average age 50 v. 58 yr, p =0.004), had higher BMI (28.9 v. 24.6, p=0.01) compared to those with photopenic BPU. Marked specimens were composed of a higher proportion of epithelium (mean area 2.6 v. 0.4 mm2, p=<0.001), lower proportion of stroma (7.6 v. 11.6 mm2, p=0.005), and similar proportion of fat (3.7 v. 3.9 mm2, p=0.41) compared to photopenic specimens.

Marked specimens also contained a higher number of lobules on average (15.5 vs. 6.3, age-adjusted p=0.0012). Photopenic specimens were more likely to exhibit complete lobular involution (age-adjusted p<0.0001). Ki-67 expression was higher in marked specimens compared to photopenic (8.5% vs. 2.6%, p = 0.006) but did not differ between groups after adjustment for area of epithelium (p=0.26). Estrogen receptor-alpha expression did not differ (27.2% vs. 31.8%, p = 0.12) between sample groups.

Conclusion:
Findings suggest that BPU on MBI reflects the proportion of epithelium compared to stroma and lobular involution status of breast fibroglandular tissue.

The Relationship Between Long and Short Term Weight Change and Mammographic Density in a UK Diet Intervention Study

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Purpose:
Adult weight gain is associated with an increased risk of postmenopausal breast cancer but its relationship with mammographic density is less clear. We investigated the relationship between density and long-term weight change since age 20y and short-term BMI change during a dietary intervention, as well as cross-sectional associations between density and BMI across the intervention.

Method:
Our analysis included 65/74 women recruited to a one year weight-loss intervention in Manchester, UK. These women were overweight, premenopausal, aged 35-45y, with a family history of breast cancer. Weight, BMI, dense area (Cumulus) and volume (Manchester Stepwedge) were available at baseline, 1y and 2y during the intervention. Long-term weight change was calculated as the difference between weight age 20y (assessed by questionnaire) and mean weight across the intervention. A linear mixed model tested the effect of long-term weight change on density, adjusted for age and BMI. Repeated-measure correlation coefficients assessed cross-sectional associations between density and BMI, and the effect of short-term dietary BMI change on density.

Results:
Long-term weight gain since 20y was significantly and positively associated with dense area (P=0.0011) but not dense volume (P=0.08) or breast fat (area P=0.17, volume

P=0.30).

Cross-sectional BMI across the intervention was not significantly correlated with dense area (-0.12 (P=0.18)), but was significantly correlated with dense volume (0.41 (P=0.0003)) and breast fat (area 0.74 (P<0.0001), volume 0.77 (P<0.0001)).

Short-term BMI change during the intervention was not significantly correlated with dense area (0.01 (P=0.90)) or dense volume (0.08 (P=0.43)), but was strongly correlated with breast fat (area 0.45 (P<0.0001), volume 0.58 (P<0.0001)).

Conclusion:
Women with greater long-term weight gain since age 20y were more likely to have higher amounts of dense tissue. Short-term dietary weight loss reduced the amount of mammographic fat, but did not change the amount of dense tissue. Results are affected by sample size and study limitations.

Impact of Oral and Transdermal Hormone Therapy on Mammographic Density in the Kronos Early Estrogen Prevention Study (KEEPS)

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Purpose:
Many clinicians have embraced low-dose hormone therapy to treat menopausal symptoms so as to mitigate the breast cancer risk associated with higher dose regimens. Data are scarce, however, regarding effects of these alternative formulations on breast cancer and its surrogate endpoints.

Method:
We conducted an ancillary study in the Kronos Early Estrogen Prevention Study (KEEPS) double-blinded randomized clinical trial to assess whether low-dose regimens of estrogen with cyclic micronized progesterone therapy are associated with increased mammographic density (MD). Among 727 recently postmenopausal women ages 42 to 58 at randomization, baseline film or digital mammogram data were available for 382 women (119 assigned to 0.45mg oral conjugated equine estrogens [o-CEE], 124 to 50 mcg transdermal estradiol [t-E2], and 139 to placebo). MD was additionally assessed at one year post-randomization. We used linear regression to evaluate intention-to-treat effects between hormonal interventions and change in MD.

Results:
There were 122 women with MD measurements assessed from film mammograms at baseline and year one. Neither o-CEE (percent density difference [PDD]: - 0.94; 95% CI: - 3.37-1.47) nor t-E2 (PDD: 0.95; 95% CI: - 1.61-3.52) relative to placebo was associated with change in MD as assessed by film. Digital mammograms were obtained at baseline and year one for 125 women. We found a suggestive but nonsignificant association for t-E2 (PDD: 2.62; 95% CI: - 0.41-5.65) relative to placebo with change in percent density and little evidence of association for o-CEE (PDD: 0.44; 95% CI: - 2.75-3.63). The absolute magnitude of PDD for all analyses was reduced relative to an evaluation of 0.625mg o-CEE in an ancillary study of the Women's Health Initiative.

Conclusion:
While these analyses lacked sufficient power to achieve precise conclusions, our results suggest that low-dose hormone therapy may not strongly affect percent MD among recently postmenopausal women. Future studies should evaluate longer term changes and other formulations of therapy.

Breast Cancer Risk Prediction: An Update to the Rosner-Colditz Breast Cancer Incidence Model

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Purpose:
To update and expand the Rosner-Colditz breast cancer incidence model by evaluating the contributions of more recently identified risk factors as well as predicted percent mammographic density (MD) to breast cancer risk.

Method:
Using data from the Nurses' Health Study (NHS) and NHSII, we added adolescent somatotype (9 unit scale), vegetable intake (servings/day), breastfeeding (months), physical activity (MET-hrs/week), and predicted percent MD to the Rosner-Colditz model to determine whether these variables improved model discrimination. We evaluated all invasive as well as ER+/PR+, ER+/PR-, and ER-/PR- breast cancer.

Results:
In the NHS/NHSII, we accrued over 5,200 cases of invasive breast cancer over more than 20 years of follow-up with complete data on the risk factors. Adolescent somatotype and predicted percent MD significantly improved the original Rosner-Colditz model for all invasive breast cancer (change in age-adjusted AUC=0.020, $p<0.001$). The relative risk (RR) of invasive breast cancer for a 4-unit increase in adolescent somatotype was 0.62 (95%CI: 0.56, 0.70) whereas the RR for a 20-unit increase in predicted percent MD was 1.32 (95%CI: 1.28, 1.36). Adolescent somatotype and predicted percent MD also significantly improved the ER+/PR+ model (change in age-adjusted AUC=0.020, $p<0.001$) as well as the ER+/PR- model (change in age-adjusted AUC=0.012, $p=0.007$). Adolescent somatotype, predicted percent MD, breastfeeding, and vegetable intake improved the ER-/PR- model (change in AUC=0.031, $p<0.0001$). The RR of ER-/PR- disease for 5 vegetable servings/day increase was 0.83 (95%CI: 0.70, 0.99), while the RR for every 12 months of breastfeeding was 0.88 (95%CI: 0.77, 1.01). Physical activity did not improve risk classification in any model.

Conclusion:
Adolescent somatotype and predicted percent MD significantly improved breast cancer risk classification using the Rosner-Colditz model. Further, risk factors specific to ER- disease, such as breastfeeding and vegetable intake, may also help improve risk prediction of this aggressive subtype.

Development of Cell-Free Nucleic Acid-Based Tests for Detection of Invasive Breast Cancer: The STRIVE Study

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Purpose:
Circulating cell-free nucleic acids (cfNAs) isolated from peripheral blood and analyzed with high-intensity sequencing have potential for early cancer detection. Development of cfNA-based tests for this purpose will require well-annotated cohorts of asymptomatic participants with adequate volumes of prediagnostic blood. The STRIVE Study cohort was recently established for the training and validation of cfNA-based tests for early detection of breast cancer.

Method:
The STRIVE Study is a new prospective, multi-ethnic mammography cohort that will recruit 120,000 women from at least 15 breast cancer screening centers across the US. Participants are recruited within 28 days of a routine screening mammogram (digital or tomosynthesis), provide consent, give 4 x 10 mL blood samples and complete an online risk factor questionnaire at their convenience. Participants will be followed for all cancer diagnoses, recurrence and death for at least 5 years. Pertinent medical record information (including breast density and other mammography results) and follow-up will be transferred electronically to a central database throughout the study period. Additional blood samples will be collected from participants with abnormal mammograms or diagnosed with cancer to document and better understand the evolution of the cfNA signal.

Results:
Recruitment began in February 2017. Preliminary participant characteristics will be presented.

Conclusion:
The STRIVE Study will be used to train and validate new cfNA tests for early detection of breast cancer and pan-cancer. In conjunction with breast imaging, cfNA-based tests have the potential to improve detection in women with dense breast tissue. In addition, the cohort will be an important new resource for studying the performance of contemporary screening and diagnostic mammography among population subgroups.

Participation in the Second Round of the DENSE Trial on MRI Screening for Women with Extremely Dense Breasts

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Purpose:
To determine what proportion of women keeps participating in MRI screening after having experienced one MRI examination in a trial on supplemental screening in women with extremely dense breasts (DENSE).

Method:
The participation in the second screening round was assessed among 3,873 women who had their first MRI screening round two years earlier. To be eligible for the second round, participants needed to have undergone another negative routine screening mammography. Continuing participants were compared to participants who stopped after one round for their experiences with their first MRI screening (screen-specific items (SSI) questionnaire). We also analyzed reported reasons for stopping participation.

Results:
Of 3,873, 9% were not eligible for the second MRI examination (7% did not return to regular screening, 1.5% had a positive mammography result, 0.5% passed away). 81% of eligible women (n=3,516) participated in the second round, 4% did not want to participate now, but likely in a following round, and 15% no longer wanted to participate (stopping participants).
Women who stopped participating had the same median age as the continuing participants (54 years). They reported somewhat higher scores on the SSI questionnaire compared to continuing participants. 11.4% of stopping participants experienced (some, quite or heavy) pain, 64.9% any discomfort, and 22.1% any anxiety during the first MRI screening; this was respectively 9.9%, 64.2%, and 20.6% in the continuing participants. Most frequently mentioned reasons for stopping were MRI-related (e.g. claustrophobia, pain or MRI noise) (31%), time-related (20%), personal (17%), or contrast-related (10%).

Conclusion:
The majority of women with extremely dense breasts, invited for a second MRI

examination continues participation. Experiences of pain, discomfort or anxiety right after the first MRI had been reported only slightly more often by stopping participants, but did play a role in the decision to stop, together with time-related and personal reasons.

Application of ATLAS.Ti Qualitative Data Analysis Software and Ockham's Razor to High Mammographic Breast Density (HMBD) Hypotheses

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Purpose:
To generate a new hypothesis and accelerate therapeutic interventions into the prevention of HMBD by drawing attention to the narrative employed by public cancer entities.

The new hypothesis is:
If HMBD is not normal, and HMBD increases the morbidity/mortality from breast cancer, then it is desirable to:
a) Avoid HMBD in the first place
b) Reduce HMBD to reduce breast cancer morbidity/mortality.

Method:
73 well-recognised international cancer and breast cancer organizations' websites were searched for narrative about HMBD and the implication that HMBD is normal. Seven key words and five key-word phrases implying normality of HMBD were coded into ATLAS.ti qualitative data analysis software and analysed for rich and thick implication of HMBD normality.

Results:
54 organizations used rich and thick narrative to imply that HMBD was normal.
19 organizations did not mention HMBD.
No organizations implied HMBD was not normal.

Conclusion:
High definition mammography has only been available for 15 years, it is not possible to make the statement that HMBD is normal; it can only be stated that it is currently common. Thus the HMBD normality hypothesis cannot be proven.

Applying Ockham's Razor, the hypothesis that HMBD is normal must be rejected as it can not be proven. Therefore it is anticipated that the hypothesis HMBD is not normal will result in more rapid development of preventative and therapeutic interventions.
If this new hypothesis is not accepted, HMBD research could result in a similar research trajectory as high lipids and heart disease. The hypothesis that high lipids were not normal was rejected from 1905 until the 1970's and therapeutic intervention only occurred in the 1980s.

Title of Abstract: Using a Polygenic Risk Score and Breast Density to Predict Interval Cancers

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Purpose: Interval cancers present symptomatically between screening rounds following a normal mammogram and tend to have poor prognostic features like estrogen receptor (ER) negativity and increased proliferation. While having dense breasts increases one's risk for interval cancers, other risk factors are poorly understood. Polygenic risk scores (PRS) based on a composite of multiple single nucleotide polymorphisms (SNPs) predict overall breast cancer risk but are not optimized to identify interval cancers. We identified SNPs associated with poor prognostic features of breast cancers with the hypothesis that a PRS comprised of these SNPs would better predict interval cancers. We then compared the performance of the PRS with breast density in an independent screening dataset.

Method: We developed our PRS using case-case analysis within The Cancer Genome Atlas (TCGA). Principal components (PC) analysis of gene-expression data was used to identify PCs associated with ER-negativity and proliferation after adjustment for ancestry. SNPs with reported genome-wide association with breast cancer were selected for the PRS based on the directionality and significance of associations with poor prognosis PCs in linear regression. We then tested the discrimination of the PRS in a nested case-control study of women screened at California Pacific Medical Center. Logistic regression was used to evaluate associations of PRS and breast density (BI-RADS) with interval cancers, and area under the receiver operating characteristic curve (AUROC) was calculated for respective models.

Results: To select a subset of SNPs predictive of interval cancer, we evaluated the associations of candidate SNPs with negative prognostic features of breast cancer in TCGA. In principal components analysis of 12,659 gene expression transcripts from 1,024 invasive breast cancers, PC1 recapitulated ER status while PC3 recapitulated proliferation. SNPs associated with ER-negativity or increased proliferation were selected for the PRS. We tested the association of the PRS and breast density with interval cancers in an independent dataset of 496 controls and 471 cases (369 screen-detected, 102 interval cancers). BI-RADS density, adjusted for age and BMI, was strongly associated with interval cancers vs controls (OR 4.27, 95% CI 2.03-8.99 for BI-RADS d vs b) with AUROC of 0.65 (95% CI 0.59-0.71). The PRS was weakly associated with interval cancer status relative to controls but did not substantially improve discrimination when combined with density.

Genome-Wide Association Study Identifies Novel Loci for Mammographic Breast Density

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Purpose:
Mammographic density is a strong risk factor for breast cancer. Most of the variation in mammographic density is explained by hereditary factors that remain largely unknown. We conducted a genome-wide association study to identify novel loci for mammographic density.

Method:
This study included 24,192 non-Hispanic white women genotyped on the Affymetrix Axiom European array as part the Research Program on Genes, Environment and Health (RPGEH). All women were 40 years or older and underwent screening with full-field digital mammography at 37 Kaiser Permanente clinics throughout Northern California. Density measurements were obtained by a single radiological technologist using Cumulus on the processed images. In Stage 1, 20,311 women imaged using Hologic machines were analyzed. In Stage 2, 3881 additional women imaged using GE machines were analyzed independently. Meta-analysis was performed using METAL.

Results:
Combined analysis of Stages 1 and 2 identified 37 loci associated with dense area (n = 24), non-dense area (n = 15) or percent dense area (n = 16) with p-values < 5 × 10^-8 and concordant associations in Stages 1 and 2. Interestingly, alleles at 3 loci were associated with dense area and non-dense area in the same direction, and consequently were not significantly associated with percent dense area. Among the 37 loci, 10 overlapped with known susceptibility alleles for breast cancer and 8 were previously known to be associated with mammographic density.

Conclusion:
Mammographic density is a complex trait influenced by polygenic and environmental factors. We found evidence that some loci have pleiotropic effects on the amount of dense and fatty tissue in the breast, and many loci are also associated with breast cancer. Further analyses are needed to identify potentially functional variants, and biological pathways that may be involved in mammographic density.

Title of Abstract: Integrating Breast Density and SNP scores into the Tyrer-Cuzick Model

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Purpose: There are a number of models currently available to assess the risk of developing breast cancer using classical risk factors. Of them the Tyrer-Cuzick (TC) model, which was originally developed to assess risk for women going into the IBIS breast cancer prevention trials, is one of the more widely used and accurate models. Version 8 has added breast density and a SNP score to improve accuracy. Here we review progress towards this goal.

Method: A major challenge is that breast density was originally assessed on film images and most risk estimates are based on that measure. Most mammograms are now digital and newer methods have been developed for that including volumetric measures such as the automated Volpara estimate. We review these measures and discuss how they can be added to the TC risk model which uses other well established factors. Density data from the PROCAS (Manchester) screening cohort, the KARMA (Sweden) study, the University of Virginia (UVa) and the BCSC (Washington) cohort, as well as SNP data from PROCAS and the IBIS-I and Marsden prevention trials in high risk women will be presented, and different methods of assessing breast density compared. A combined analysis of both factors in the PROCAS study will also be presented.

Results: Density was measured by a visual analog scale and by Volpara in PROCAS, and both added a substantial amount of information to TC. For the visual scale the interquartile odds ratio (IQ-OR) was 1.48 vs 1.36 for TC. The two measures were largely independent with an IQ-OR for density of 1.47 when added to TC. Very similar results were seen for volumetric density. Volumetric density by Volpara was also measured in KARMA and UVa cohorts, with very similar results. Density was measured by the 4 category Bi-Rads scale (4th edition) in the UVa and BCSC cohorts, again with similar additive predictive value. An 88 SNP score was evaluated in the combined IBIS-I and Marsden breast cancer prevention trials in high risk women using the OncoArray. A significant improvement in risk prediction was seen (IQ-OR = 1.37) which was similar to that obtained from the TC model (IQ-OR = 1.45). However the calibration was poor (slope of observed vs expected events 0.46) with greater predicted than actual separation. SNP88 was independent from the TC risk and their use in combination gave substantially better risk assessment (IQ-OR = 1.65). No interaction with treatment was seen. SNP 18 was evaluated in the PROCAS study where it had an IQ-OR of 1.65, with no correlation with TC and an excellent calibration (slope 1.00). Lastly both visual density and SNP18 were evaluated in PROCAS and were found to be independent, with both adding to the risk discrimination provided by TC. When used together the number of women found to

be at a greater than an 8% 10y risk (which is the NICE guideline cut-off for offering preventive treatment) was substantially increased.

Conclusion: Both breast density and a SNP score add substantial and clinically relevant information about breast cancer risk to the classical factors in previous version of the Tyrer-Cuzick model. Thei use will facilitate adoption of risk assessment for both risk adapted screening algorithms and in determining who will benefit most from preventive strategies. Work on identifying low risk women who need less or no routine screening is less advanced but remains an important goal of this work.

Evaluation of the Tyrer-Cuzick Breast Cancer Risk Model of with BIRADS Density in a Screening Cohort from Washington State

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Purpose:
To assess the predictive ability of the Tyrer-Cuzick breast cancer risk model in a screening cohort, with and without incorporating BI-RADS breast density.

Method:
Women aged 40-73y attended at least two screening visits in the Kaiser Permanente Washington (formerly Group Health) Breast Cancer Surveillance registry between 1996-2013 and did not have breast cancer before or at the initial screen; a risk questionnaire was completed at each screening visit. Follow up was from six months after baseline mammogram (screen-negative) to the earliest of age 75y, year 2014, six months after the last mammogram, or diagnosis of ductal carcinoma insitu or invasive breast cancer (obtained through tumor registry linkage). We predicted invasive breast cancer incidence after the first visit, updating risk factor data with each new questionnaire. A pre-defined algorithm combined density with the Tyrer-Cuzick model. We compared the observed (O) number of cancers with expected (E) predictions using 95% Poisson model confidence intervals. We measured predictive ability using the likelihood-ratio $\chi 2$ (LR-$\chi 2$) from a proportional-hazards model with log 10y risk at baseline.

Results:
From 105558 women, 2877 were subsequently diagnosed with invasive breast cancer after a median 7.4ys follow up (annual incidence rate (AIR) 3.2 per 1000 women). Overall calibration was good (O/E 1.02 95%CI 0.98-1.06). The model at baseline identified 2228 (2.1%) women to be at high risk (8%+ 10y risk), of whom 159 subsequently developed invasive breast cancer (O/E 0.96, 95%CI 0.82-1.12, AIR 9.7). Combining breast density with Tyrer-Cuzick improved predictive power by ~50% (LR-$\chi 2$ from 496 to 754) and identified many more high-risk women (3986, 3.8% women, 291 cancers, O/E 0.93 (0.83-1.05), AIR 10.0).

Conclusion:
BI-RADS breast density substantially improves the ability of risk models to accurately identify high risk women.

Population-Based Assessment of the Effect of MRI Background Parenchymal Enhancement on Future Primary Breast Cancer Risk

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Purpose:
To evaluate the effect of background parenchymal enhancement on future risk of breast cancer among women undergoing breast MRI in the US population-based Breast Cancer Surveillance Consortium (BCSC).

Method:
In this IRB-approved and HIPAA-compliant prospective cohort study, data from five BCSC breast imaging registries were collected on women who underwent breast MRI with qualitative measurement of BPE between 2005-2014. Women were included if BPE was measured more than 3 months prior to her first diagnosis of invasive breast cancer or ductal carcinoma in situ (DCIS), using the baseline BPE measurement assigned. Cancer outcomes were ascertained through linkages with state or regional cancer registries and pathology databases. Risk of breast cancer associated with BPE was estimated using a Cox proportional hazards model stratified by BCSC registry and adjusted for age and type of MRI examination (screening versus diagnostic).

Results:
A total of 3,223 women were included, of whom 100 women developed cancer (71 invasive, 29 DCIS) during an average of 2.5 years of follow-up. Cases had a higher proportion of pre-menopausal women (41% versus 33%) and first-degree family history (59% vs. 51%). When using four ordinal categories of BPE with minimal BPE as reference, increasing levels of BPE were associated with significant or near significantly increasing cancer risk: mild BPE hazard ratio (HR) 1.66 (95% confidence interval (CI) 0.93, 2.96), moderate BPE HR of 2.23 (95% CI 1.25, 3.96) and marked BPE HR of 3.35 (95% CI 1.82, 6.16). When dichotomizing BPE using minimal BPE as reference, women with mild, moderate, or marked BPE had a significantly increased risk of cancer (HR 2.17, 95% CI 1.33, 3.55). Subgroup analysis using dichotomized BPE showed similar effects among women stratified by mammographically fatty/scattered fibroglandular breasts (HR 2.19, 95% CI 0.84, 5.70) and heterogeneous/extremely dense breasts (HR 1.93, 95% CI 0.99, 3.77). Dichotomized BPE significantly increased risk of invasive cancer (HR 2.44, 95% CI 1.35, 4.39), but associations with DCIS were weaker and not statistically significant (HR 1.61, 95% CI 0.66, 3.91).

Conclusion:
We found BPE is a predictor of future breast cancer risk independent of breast density and with stronger associations with invasive cancer than DCIS.

Conclusion: Breast density is associated with development of interval cancers. While we were able to construct a PRS comprised of SNPs associated with poor prognostic features, it had limited predictive value beyond that of density.